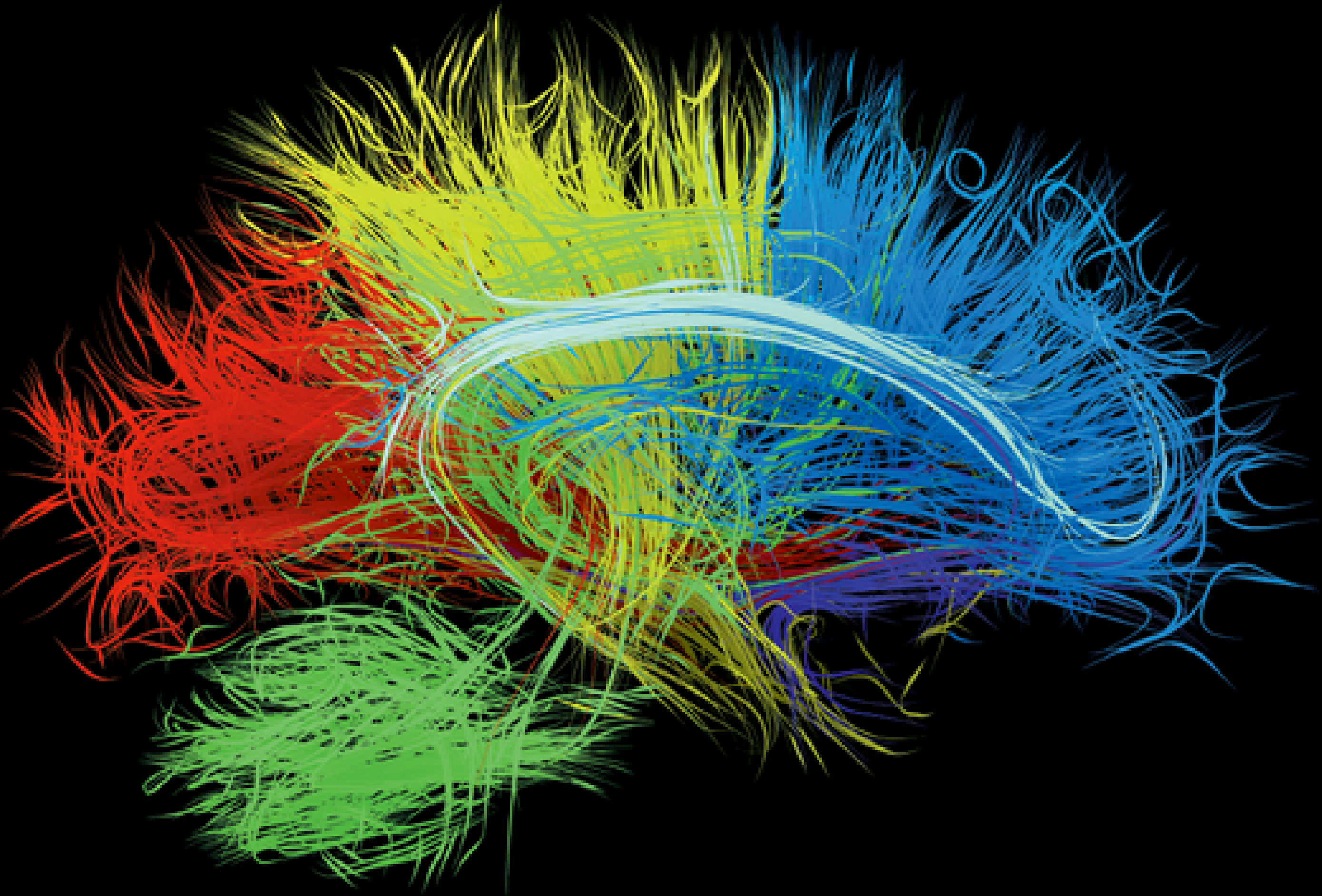

# NEUROLOGY BOARD REVIEW

## Questions and Answers, Second Edition

AMY McGREGOR, NORIMITSU KUWABARA,
RENA D. SUKHDEO SINGH, CHILVANA PATEL

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## QUESTIONS AND ANSWERS

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SECOND EDITION

BY

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*Dedication by Amy McGregor*

*For my son, Matthew; all my nonbiological children; and my nonbiological sister, Lisa*

# NOTE FROM THE AUTHOR FROM THE FIRST EDITION

This book was designed to prepare the reader for the American Board of Psychiatry and Neurology (ABPN) board certification and recertification exams. It covers the topics listed on the content outline provided by the ABPN. I recommend that you personally review this document prior to your test. This book is not a clinical manual and is not intended to guide clinical decision-making or treatment; it is designed for test preparation. In order to convey important information, I have used some question formats that will not be on the actual ABPN board exam. I strongly recommend that you check the ABPN website for the format of your test and review the information provided by the testing site, including any practice questions. This is a very different test than the resident in-service training (RITE) exam. I also suggest that you take advantage of the excellent resources provided by the American Academy of Neurology. Best of luck on your exam!

—AM

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# 1.

# AUTONOMIC NERVOUS SYSTEM

## QUESTIONS

**1. State whether each of the following is a sympathetic or a parasympathetic response.**

1) Pupil constriction
2) Inhibition of digestion
3) Stimulation of glucose release
4) Systemic vasoconstriction
5) Salivation
6) Bronchodilation
7) Lacrimation
8) Intestinal vasodilation

**2. Which of the following is not involved in the parasympathetic nervous system?**

A. Oculomotor nerve
B. Facial nerve
C. Trigeminal nerve
D. Glossopharyngeal nerve

**3. Which of the following is a part of the sympathetic nervous system?**

A. Superior cervical ganglia
B. Otic ganglia
C. Pterygopalatine ganglia
D. Submandibular ganglia

**4. Which cranial nerve innervates the chemoreceptors and baroreceptors of the carotid body?**

A. Trigeminal
B. Facial
C. Glossopharyngeal
D. Vagus

**5. Most parasympathetic preganglionic fibers for the heart, lungs, and gastrointestinal tract arise from which of these structures?**

A. Dorsal motor nucleus of the vagus
B. Nucleus tractus solitarius
C. Nucleus ambiguus
D. Trigeminal nucleus

**6. Which neurotransmitter is released by parasympathetic preganglionic neurons?**

A. Acetylcholine
B. Norepinephrine
C. Epinephrine
D. Glycine

**7. Which neurotransmitter is released by sympathetic preganglionic neurons?**

A. Acetylcholine
B. Norepinephrine
C. Epinephrine
D. Glutamate

**8. Which neurotransmitter is released by most sympathetic postganglionic neurons?**

A. Acetylcholine
B. Norepinephrine
C. Epinephrine
D. Glutamate

**9. True or false?**

During urination, the sympathetics are inhibited, causing relaxation of the bladder neck, and the parasympathetics are activated, causing contraction of the detrusor muscle.

**10. A patient has a suspected small-fiber neuropathy with autonomic dysfunction. Which of the following tests is the most sensitive?**

A. Sudomotor testing
B. Electromyography and nerve conduction studies (EMG/NCS)
C. Holter test
D. Tilt table test

**11. A 60-year-old man presents with fatigue and falls. On review of systems, he reports constipation and bruising. Neurologic examination identifies a peripheral neuropathy. General examination identifies macroglossia, hepatomegaly, and ecchymoses. Which test is most likely to confirm the diagnosis?**

A. Immunofixation electrophoresis
B. Kidney biopsy
C. Liver biopsy
D. Glucose tolerance test

**12. A 45-year-old woman presents with multiple falls. Which of the following would be most helpful in ruling out dysautonomia as the cause?**

A. Denial of lightheadedness
B. A history of constipation
C. A history of urinary urgency
D. A normal tilt table test

**13. A 15-year-old girl presents with lightheadedness, headaches, and fatigue that began after a viral illness. With minimal activity, she develops palpitations and sweating. When sitting, her heart rate is 80 beats per minute (bpm). Her heart rate increases to 120 bpm after she stands. Her blood pressure does**

**not change significantly. What is the most likely diagnosis?**

A. Diabetes
B. Orthostatic hypotension
C. Postural orthostatic tachycardia syndrome (POTS)
D. Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) syndrome

**14. A patient with suspected autonomic dysfunction performing the Valsalva maneuver does not demonstrate the normal increase in blood pressure during phase 4. What does this finding suggest?**

A. Orthostatic hypotension
B. Parkinson disease
C. Parasympathetic dysfunction
D. Sympathetic dysfunction

**15. True or false?**

A patient with anhidrosis on thermoregulatory sweat testing and a normal result on quantitative sudomotor autonomic reflex testing has a preganglionic sudomotor abnormality.

**16. Which of the following is associated with autonomic neuropathy?**

A. Anti-Hu antibodies (also known as antineuronal nuclear antibody type 1 [ANNA-1])
B. Nicotinic ganglionic acetylcholine receptor ($\alpha_3$-AChR) antibodies
C. P/Q-type calcium channel antibodies
D. All of the above

**17. Which of the following can cause autonomic neuropathy?**

A. Chagas disease
B. Diphtheria
C. Leprosy
D. All of the above

**18. What is the most common manifestation of autonomic dysreflexia?**

A. Arrhythmia
B. Hypertension
C. Hypoglycemia
D. Tachypnea

**19. Which of the following structures is involved in conscious bodily sensation, taste, and cardiovascular regulation?**

A. Amygdala
B. Angular gyrus
C. Cingulate cortex
D. Insular cortex

**20. Which of the following is involved with dilatation of cranial and visceral vessels?**

A. Epinephrine
B. Nitric oxide
C. Norepinephrine
D. Vasoactive intestinal peptide

**21. Which of the following is *least* likely to cause anhidrosis?**

A. Acetazolamide
B. Bupropion
C. Cyproheptadine
D. Diphenhydramine
E. Zonisamide

**22. Which of the following is more likely to occur in baroreflex failure than in autonomic failure?**

A. Labile hypertension
B. Orthostatic hypotension
C. Postprandial hypotension
D. Supine hypertension

**23. Which of the following is mediated by premotor neurons in the rostral ventrolateral medulla?**

A. Beat-to-beat control of heart rate
B. Cardiac output
C. Inhibition of secretion of arginine vasopressin by the hypothalamus
D. Vasoconstriction of muscle, mesenteric, and renal blood vessels

**24. Which of the following is *least* consistent with diabetes?**

A. Cranial nerve III palsy with pupil dilation
B. Distal symmetric polyneuropathy
C. Gustatory sweating and gastroparesis
D. Lumbosacral radiculoplexus neuropathy

**25. Which of the following is *least* likely to be associated with significant autonomic dysfunction?**

A. Chronic inflammatory demyelinating neuropathy (CIDP)
B. Cyclic vomiting syndrome
C. Intestinal pseudo-obstruction
D. Multiple system atrophy
E. Sjögren syndrome

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# AUTONOMIC NERVOUS SYSTEM

## ANSWERS

1. **Sympathetic or parasympathetic responses**

    1) Pupil constriction—Parasympathetic
    2) Inhibition of digestion—Sympathetic
    3) Stimulation of glucose release—Sympathetic
    4) Systemic vasoconstriction—Sympathetic
    5) Salivation—Parasympathetic
    6) Bronchodilation—Sympathetic
    7) Lacrimation—Parasympathetic
    8) Intestinal vasodilation—Parasympathetic

    (See Table 1.1.)

*Table 1.1* FUNCTIONS OF THE SYMPATHETIC AND PARASYMPATHETIC NERVOUS SYSTEMS

| SYMPATHETIC | PARASYMPATHETIC |
|---|---|
| **Pupil dilation** | **Pupil constriction** |
| **Increased heart rate and contraction** | **Decreased heart rate** |
| **Inhibition of digestion** | **Stimulation of digestion** |
| **Bronchodilation** | **Bronchoconstriction** |
| **Ejaculation** | **Erection** |

The parasympathetic nervous system is also known as the craniosacral division of the autonomic nervous system.

The preganglionic neurons of the sympathetic nervous system are in the intermediolateral nucleus (T1–L2) of the spinal cord.

2. **C**

The oculomotor, facial, glossopharyngeal, and vagus nerves are part of the parasympathetic nervous system; the trigeminal nerve is not.

The oculomotor nerve causes constriction of the pupil and ciliary body.

The facial nerve causes lacrimation and salivation.

The glossopharyngeal nerve causes salivation.

The vagus nerve causes heart deceleration, bronchoconstriction, stimulation of digestion by the stomach and release of bile from the gallbladder, and vasodilation of intestinal blood vessels.

3. **A**

The superior cervical ganglia are part of the oculosympathetic pathway. They are involved in pupil dilation.

4. **C**

The glossopharyngeal nerve innervates the chemoreceptors and baroreceptors of the carotid body. Information regarding blood volume and blood pressure from mechanoreceptors in the carotid arteries is relayed to the nucleus tractus solitarius (NTS) via the glossopharyngeal nerve. Similar information is carried from the aorta to the NTS through the vagus nerve.

Glossopharyngeal neuralgia causes pharyngeal pain. It can also result in reflex bradycardia and syncope.

5. **A**

Motor fibers within the vagus nerve arise from the dorsal motor nucleus of the vagus or from the nucleus ambiguus. Most parasympathetic preganglionic fibers for the heart, lungs, and gastrointestinal tract arise from the dorsal motor nucleus of the vagus.

The dorsal motor nucleus of the vagus receives information from the NTS. The NTS is the main visceral afferent nucleus in the brainstem. It receives cardiovascular, respiratory, and gastrointestinal afferents in cranial nerves IX and X. It also receives taste information from cranial nerves VII, IX, and X.

The nucleus ambiguus, which is in the medulla, does contain preganglionic parasympathetic neurons, but fewer than are found in the dorsal motor nucleus. The nucleus ambiguus also supplies fibers that innervate the stylopharyngeus via the glossopharyngeal nerve and that innervate muscles of the soft palate, pharynx, and larynx via the vagus nerve. (The tensor veli palatini is supplied by cranial nerve V.)

6. **A**

Acetylcholine is released by parasympathetic preganglionic neurons.

7. **A**

Acetylcholine is released by sympathetic preganglionic neurons.

8. **B**

Norepinephrine is released by most sympathetic postganglionic neurons. Sweat glands are an exception. Postganglionic neurons of sweat glands release acetylcholine; postganglionic sympathetic sweat glands have muscarinic receptors.

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**9. True**

The overall effect of sympathetic autonomic innervation of the bladder is inhibition of micturition. Sympathetic fibers innervate the internal sphincter and the detrusor muscle. Sympathetic activation results in contraction of the internal sphincter. It also causes relaxation of the detrusor muscle, which allows the bladder to fill.

The parasympathetic nervous system promotes urination. The parasympathetic nervous system causes contraction of the detrusor muscle, which leads to bladder emptying.

The external sphincter is under somatic control. It relaxes during micturition.

**10. A**

Sudomotor testing is sensitive to autonomic dysfunction associated with small-fiber neuropathy. EMG/NCS do not assess the appropriate nerve fibers and therefore miss small-fiber neuropathies. Skin biopsy is the gold standard for diagnosing small-fiber neuropathy.

**11. A**

This is primary amyloidosis, which causes autonomic neuropathy. Immunofixation electrophoresis can confirm the diagnosis.

The most common types of amyloidosis are primary amyloidosis, which is caused by a monoclonal gammopathy, and familial amyloidosis, which is caused by mutations in transthyretin.[1]

Patisiran is a treatment for the polyneuropathy associated with hereditary transthyretin-medicated amyloidosis. It is a double-stranded small interfering ribonucleic acid. It can reduce vitamin A levels.

**12. D**

A normal tilt table test result would be the most helpful finding in ruling out dysautonomia. Patients with autonomic disorders do not always complain of lightheadedness. Constipation and urinary urgency can occur with dysautonomia.

**13. C**

This case is most consistent with postural orthostatic tachycardia syndrome (POTS), which is a type of orthostatic intolerance. Orthostatic intolerance is the inability to tolerate upright posture due to symptoms resulting from cerebral hypotension and/or sympathetic activation that improve with lying down.[2]

The normal vital sign response to standing is mediated by the baroreflex. There is a slight decrease in systolic blood pressure, slight increase in diastolic blood pressure, and slight increase in heart rate.

Orthostatic hypotension is defined by a decrease in systolic blood pressure of at least 20 mm Hg and/or a decrease in diastolic blood pressure of at least 10 mm Hg in the first 3 minutes of standing. If this decrease is not present but the patient has tachycardia and is symptomatic, then the patient has orthostatic intolerance. In adults with POTS, the heart rate increases by at least 30 bpm when standing. In children with POTS, it can increase by 40 bpm. POTS symptoms may manifest after an illness. Joint hypermobility may be seen on exam.[2] Treatment involves hydration, increased salt intake, conditioning and strengthening, and sometimes support stockings. Medications used to treat POTS include β-blockers, midodrine, and fludrocortisone. Fludrocortisone has mineralocorticoid activity. Midodrine is a sympathomimetic (alpha-1 agonist) that can cause supine hypertension, but it does not cause fluid retention like mineralocorticoids can.

ROHHAD syndrome manifests in early childhood with rapid weight gain in a previously normal child. Autonomic dysfunction then occurs, followed by hypoventilation, which can be fatal. In addition to weight gain, polydipsia and hypernatremia are other common manifestations of hypothalamic dysfunction in patients with ROHHAD syndrome. Autonomic dysfunction causes thermal dysregulation, gastrointestinal dysmotility, and ophthalmologic findings such as pupillary abnormalities. Some patients with ROHHAD syndrome develop neural crest tumors. ROHHAD syndrome shares some features with congenital central hypoventilation syndrome (CCHS), but CCHS is associated with mutations in *PHOX2B*.[3]

**14. D**

A lack of increase in blood pressure during phase 4 is consistent with sympathetic dysfunction. Sympathetic dysfunction can also cause an excessive decrease in blood pressure during early phase 2 of the Valsalva maneuver due to decreased peripheral vasoconstriction.

The Valsalva maneuver is a test of cardiovascular adrenergic function and cardiovagal function.

The Valsalva maneuver can be divided into four phases:

- Phase 1 occurs during the onset of strain. The increase in intrathoracic pressure causes compression of the aorta and an increase in blood pressure.
- Phase 2 begins with reduced venous return to the heart, which leads to decreased cardiac output and systolic pressure. This is followed by sympathetically mediated peripheral vasoconstriction and an increase in blood pressure and heart rate.
- Phase 3 occurs with the release of strain, resulting in decreased intrathoracic pressure and a transient decrease in blood pressure.
- Phase 4 is associated with increased stroke volume due to increased venous return to the heart. Blood is pumped into the constricted vasculature, causing a blood pressure overshoot. Due to the baroreceptor

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reflex, this overshoot with phase 4 leads to decreased heart rate via the vagus nerve.

The Valsalva ratio, which assesses heart rate changes with the Valsalva maneuver, reflects cardiovagal function/parasympathetic activity. The Valsalva ratio is calculated by max HR/min HR (maximum heart rate divided by minimum heart rate). This represents a comparison between the decreased heart rate with phase 4 and the increased heart rate during late phase 2.

The deep breathing test is also a measure of parasympathetic function. In this test, the expiratory/inspiratory (E/I) ratio is calculated. This is the ratio of the longest R-R interval during expiration divided by the shortest R-R interval during inspiration.

**15. True**

Quantitative sudomotor autonomic reflex testing (QSART) assesses the postganglionic sympathetic sudomotor axon. If the patient has anhidrosis during thermoregulatory sweat testing and the QSART is normal, the lesion is preganglionic.

**16. D**

Anti-Hu (also known as ANNA-1) antibodies can be seen in small-cell lung cancer, which is a common cause of paraneoplastic autonomic neuropathy. Small-cell carcinoma and paraneoplastic autonomic neuropathy are also associated with collapsing response mediator protein-5 (CRMP-5) antibodies, also known as CV2 antibodies.[4]

Nicotinic ganglionic acetylcholine receptor ($\alpha_3$-AChR) antibodies are seen in autoimmune autonomic ganglionopathy, which causes pandysautonomia. Orthostatic hypotension and constipation are common in these patients. Cholinergic failure and absent sensory involvement (apart from complaints of paresthesias) help differentiate autoimmune autonomic ganglionopathy from other conditions with autonomic features.

P/Q-type calcium channel antibodies occur in Lambert–Eaton syndrome (see Box 1.1).

### *Box 1.1* ANTIBODIES ASSOCIATED WITH AUTONOMIC NEUROPATHY

- Nicotinic ganglionic acetylcholine receptor (α3-AChR) antibodies
- Anti-Hu antibodies
- Purkinje cell antibodies type 2
- Collapsing response mediator protein-5 (anti-CV2)
- P/Q-type calcium channel antibodies
- *N*-methyl-D-aspartate (NMDA) receptor antibodies

**17. D**

Chagas disease (due to the parasite *Trypanosoma cruzi*) causes megaesophagus and megacolon. It can also cause orthostatic hypotension, syncope, palpitations, and sudden death.

Leprosy causes asymmetric sensory loss. Sensitivity to pain and temperature are affected first. Leprosy also can affect autonomic skin fibers, resulting in loss of sweating. Cardiac autonomic neuropathy can be seen. Nerve enlargement occurs in leprosy; nerves may be palpable.

Diphtheria causes a distal polyneuropathy involving the limbs (a symmetric sensorimotor peripheral neuropathy) and a palatal neuropathy. In addition to palatal paralysis, other cranial nerves may become involved. Patients may have a lack of accommodation with preservation of the light reflex. Involvement of the nodose ganglion of the vagus nerve can result in tachycardia. Hypotension can also occur.

Human immunodeficiency virus infection and botulism can also cause autonomic neuropathy.[1]

**18. B**

Autonomic dysreflexia can occur with lesions above T6 after the acute period. This is a sympathetic overresponse to stimuli below the level of the cord injury such as constipation, distended bladder, or skin breakdown. Hypertension is the most common manifestation. The patient may have tachycardia or bradycardia (due to the baroreflex).[5] Other common findings are headache, nausea, flushing, and blurry vision. If untreated, autonomic dysreflexia can cause intracranial hemorrhage, seizures, arrhythmia, myocardial infarction, and death.[6]

Autonomic dysreflexia is thought to be due to interruption of supraspinal descending autonomic pathways. For instance, the medulla and hypothalamus have descending inputs to preganglionic sympathetic neurons.[7]

**19. D**

The cingulate gyrus is involved in autonomic control, but it is the insula that is involved in conscious bodily sensation.[7]

The insula has multiple functions. It is the primary viscerosensory cortex. The insula receives visceral afferents with interoceptive (bodily sensation) information from the body. It has an olfactogustatory function. It is involved in processing taste stimuli.[8] The insula is also involved in cardiovascular regulation. Direct stimulation of the insula can cause changes in heart rate.[9]

Seizures arising from the insula are associated with laryngeal constriction, perioral paresthesias, dysarthria, lateralized somatosensory sensations, and focal somatomotor signs. Feelings of suffocation/breathlessness and gustatory auras are also characteristic.[10]

The amygdala is responsible for the autonomic response to emotion—for example, fear.[7]

Lesions of the angular gyrus can cause alexia with agraphia.

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**20. B**

Nitric oxide (NO) contributes to dilatation of cranial and visceral vessels. It also affects gastrointestinal motility and dilation of erectile tissue involved in penile erection.

Achalasia may be due to loss of inhibitory neurons that release NO and vasoactive intestinal peptide.[11]

**21. B**

Bupropion, which is a norepinephrine–dopamine reuptake inhibitor, tends to increase sweating. Selective serotonin reuptake inhibitors can also cause hyperhidrosis.

Carbonic anhydrase inhibitors (e.g., topiramate, acetazolamide, and zonisamide) and anticholinergic medications tend to decrease sweating.

**22. A**

Common manifestations of baroreflex failure are hypertensive crises and labile hypertension. In contrast, autonomic failure is more likely to be associated with orthostatic hypotension, postprandial hypotension, and supine hypertension. Both autonomic failure and baroreceptor failure can be associated with hypersensitivity to vasoconstrictor medications.[12]

As mentioned previously, orthostatic hypotension is defined by a decrease in systolic blood pressure of at least 20 mm Hg and/or a decrease in diastolic blood pressure of at least 10 mm Hg in the first 3 minutes of standing. Orthostatic hypotension has multiple etiologies: medications; non-neurogenic etiologies such as cardiac pump failure, reduced intravascular volume, and venous pooling; and neurogenic etiologies.[13]

Neurogenic orthostatic hypotension is due to failure of the carotid baroreflex or cardiovascular adrenergic function.[2] Neurogenic orthostatic hypotension tends to be worse in the morning, in the heat, after exercise, and after eating.[14]

**23. D**

The baroreflex affects cardiac output and peripheral resistance, which determine arterial blood pressure. Neck surgery is a potential cause of baroreflex failure.

Baroreceptor afferents from the carotid and from the aortic arch provide input to neurons in the nucleus of the solitary tract (NTS). These neurons in the NTS control peripheral resistance through a sympathoinhibitory pathway and control heart rate through a cardioinhibitory pathway.

Projections from the neurons in the NTS involved in the sympathoinhibitory pathway travel to interneurons in the caudal ventrolateral medulla. These interneurons send inhibitory projections to sympathoexcitatory neurons in the rostral ventral medulla (RVLM). The RVLM neurons send projections to the intermediolateral cell column of the spinal cord that control vasoconstriction of blood vessels. This pathway controls arterial blood pressure.

Neurons in the NTS that are involved in the cardioinhibitory pathway send projections to vagal preganglionic neurons in the nucleus ambiguus. Then, these vagal preganglionic neurons project to cardiac ganglion neurons that affect beat-to-beat control of the heart rate.[7,12]

The baroreflex also inhibits secretion of arginine vasopressin by the hypothalamus via the NTS.[12]

**24. A**

A cranial nerve III (CN 3; oculomotor nerve) palsy with pupil dilation is concerning for a posterior communicating artery aneurysm, which can compress the outer parasympathetic fibers of the nerve.

CN 3 has two major components: the outer parasympathetic fibers and the inner somatic fibers. The outer parasympathetic fibers supply the ciliary muscles and the sphincter pupillae. The inner somatic fibers supply the levator palpebrae superioris and the four extraocular muscles (superior rectus, middle rectus, inferior rectus, and inferior oblique).

Diabetes, which is associated with microvascular ischemia, is more likely to cause a pupil-sparing CN 3 palsy because the central fibers of the oculomotor nerve are more affected than the pupillomotor fibers. (The pupillomotor fibers, which travel in the more peripheral layers of the nerve, receive blood supply from the vessels around the nerve.) Of note, ocular myasthenia can also be associated with a pupil-sparing CN 3 palsy.

Diabetes also can cause light-near dissociation (the pupil reacts better with accommodation than with light).

The most common neuropathy associated with diabetes is a distal symmetric polyneuropathy. Autonomic symptoms may be present.

Diabetes is the most common cause of autonomic neuropathy. Several types of autonomic dysfunction can occur with diabetes, such as abnormalities in heart rate variability, decreased cardiac output, sudomotor dysfunction, constipation or diarrhea, reflux, voiding dysfunction, and urogenital symptoms such as erectile failure. Neuropathies associated with diabetes include generalized diabetic autonomic neuropathy, treatment-induced neuropathy, and diabetic amyotrophy. Treatment-induced neuropathy of diabetes mellitus is a painful sensory and autonomic neuropathy that can occur with rapid improvement in HgBA1c. Diabetes is also associated with a lumbosacral radiculoplexus neuropathy, which is also known as diabetic amyotrophy.[15]

**25. A**

Guillain–Barré syndrome is associated with dysautonomia, but autonomic disturbance is less likely in CIDP.

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# 2.

# BEHAVIORAL NEUROLOGY

## QUESTIONS

1. **Which of the following is the most consistent finding in delirium?**
   A. Auditory hallucinations
   B. Distractibility
   C. Aggression
   D. Seizures

2. **A patient with renal failure develops confusion. He has asterixis on examination. Head computed tomography (CT) findings are normal. Besides diffuse background slowing, what is the most likely electroencephalography (EEG) finding?**
   A. Focal slowing over the temporal lobes
   B. Focal slowing over the frontal lobes
   C. Intrusion of rapid eye movement sleep
   D. Triphasic waves

3. **A 52-year-old man with a history of migraines is brought to the emergency department because of altered mental status. On examination, he is alert and oriented to self but repeats the same questions over and over. He has anterograde amnesia, but remote memory, speech, and attention are intact. Physical examination is normal. CT and EEG are normal. Routine laboratory test results are unremarkable. Seven hours later, he recovers. What is the most likely diagnosis?**
   A. Transient global amnesia
   B. Basilar migraine
   C. Acute confusional state
   D. Postictal psychosis
   E. Wernicke–Korsakoff syndrome

4. **True or false?**
   The majority of left-handed people are left hemisphere dominant for language.

5. **Motor impersistence is suggestive of a lesion in which part of the brain?**
   A. Nondominant frontal lobe
   B. Nondominant parietal lobe
   C. Nondominant temporal lobe

6. **A right-handed patient eats food only from the right side of his plate and denies that his left arm is his. Where is the lesion?**
   A. Right frontal lobe
   B. Right parietal lobe
   C. Right temporal lobe
   D. Left frontal lobe

7. **Which lobe is responsible for identification of problems, formulations of strategies, execution of plans, and evaluation of outcomes?**
   A. Frontal
   B. Occipital
   C. Parietal
   D. Temporal

8. **Which type of memory is most likely to be affected by normal aging?**
   A. Episodic
   B. Implicit
   C. Semantic

9. **Which of the following is the most common cause of episodic memory impairment?**
   A. Alzheimer disease
   B. Parkinson disease
   C. Frontotemporal dementia
   D. Vascular cognitive impairment

10. **Which of the following is the most common cause of semantic memory impairment?**
   A. Alzheimer disease
   B. Parkinson disease
   C. Frontotemporal dementia
   D. Vascular cognitive impairment

11. **The supplementary motor area, cerebellum, and basal ganglia are critical for which type of memory?**
   A. Episodic
   B. Procedural
   C. Semantic
   D. Working

12. **Which of the following is the most common cause of procedural memory impairment?**
   A. Alzheimer disease
   B. Parkinson disease
   C. Frontotemporal dementia
   D. Vascular cognitive impairment

13. **Which lobe of the brain is primarily responsible for working memory?**
   A. Frontal
   B. Occipital
   C. Parietal
   D. Temporal

14. **A patient has impaired immediate memory, free recall, and recollection but normal item memory and cued recall. He has false memories. His memory**

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**improves significantly with environmental support. Where is his lesion?**

A. Frontal lobe
B. Lateral temporal lobe
C. Medial temporal lobe
D. Parietal lobe

**15. Which of the following is *least* likely to be seen with a lesion of the orbitofrontal cortex?**

A. Insensitive remarks
B. Akinetic mutism
C. Perseveration
D. Impulsivity

**16. Which of the following is *not* part of Balint syndrome?**

A. Simultagnosia
B. Optic ataxia
C. Optic apraxia
D. Inability to identify an object unless it moves

**17. Which of the following is caused by a lesion of the left occipital lobe and adjacent corpus callosum?**

A. Alexia with agraphia
B. Alexia without agraphia
C. Ideomotor apraxia
D. Pure word deafness

**18. A 60-year-old woman presents with difficulties writing and performing calculations. On examination, she is confused as to her left and right and has difficulty identifying fingers. Where is her lesion?**

A. Dominant inferior parietal lobe
B. Dominant superior temporal lobe
C. Nondominant inferior frontal lobe
D. Nondominant parietal lobe

**19. What is the term used when a patient believes that his friends and family have been replaced by imposters?**

A. Capgras syndrome
B. Cotard syndrome
C. Fregoli syndrome
D. Reduplicative paramnesia
E. Simultagnosia

**20. A patient with bilateral posterior cerebral artery strokes cannot see, but he denies it. What is the name of this syndrome?**

A. Anton syndrome
B. Charles Bonnet syndrome
C. Ganser syndrome
D. Geschwind syndrome
E. Klüver–Bucy syndrome

**21. Where is the lesion that causes prosopagnosia?**

A. Right parietal lobe
B. Left parietal lobe
C. Right frontal lobe
D. Bilateral occipitotemporal cortex

**22. Which lobe of the brain is tested by the Wisconsin Card Sorting Test, the Stroop Color and Word Test, and the Trail Making Test?**

A. Frontal
B. Occipital
C. Parietal
D. Temporal

**23. Which lobe is tested with go/no-go and sequencing tasks, such as the written alternating sequencing task or the manual sequencing task?**

A. Frontal
B. Occipital
C. Parietal
D. Temporal

**24. A 70-year-old woman is brought by her family to the emergency department because she is unable to speak. She obeys commands, except that she is unable to repeat when asked to do so and she cannot write. Where is the lesion?**

A. Dominant inferior frontal gyrus
B. Dominant middle frontal gyrus
C. Dominant superior frontal gyrus
D. Dominant superior temporal gyrus

**25. A patient has fluent but nonsensical speech. He also has impairments in comprehension, repetition, naming, reading, and writing. Where is the lesion?**

A. Dominant inferior frontal gyrus
B. Dominant superior temporal gyrus
C. Dominant middle temporal gyrus
D. Dominant inferior temporal gyrus

**26. A patient who has fluent speech and comprehends but cannot repeat has which of the following?**

A. Aphemia
B. Conduction aphasia
C. Transcortical motor aphasia
D. Transcortical sensory aphasia
E. Mixed transcortical aphasia

**27. A patient with global aphasia, right hemiplegia, and right hemianesthesia most likely has a stroke in which territory?**

A. Left anterior cerebral artery
B. Left middle cerebral artery
C. Inferior division of the left middle cerebral artery
D. Superior division of the left middle cerebral artery

**28. A right-handed patient has a stroke resulting in aphasia and right arm and facial weakness without sensory deficits. Which type of aphasia is most likely in this patient?**

A. Broca aphasia
B. Transcortical sensory aphasia
C. Wernicke aphasia
D. Mixed transcortical aphasia

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**29. Anomic aphasia is most likely to occur with a lesion in which region of the dominant hemisphere?**

A. Frontal operculum
B. Supplementary motor area
C. Angular gyrus
D. Inferior temporal gyrus

**30. True or false?**

Loss of emotional content of speech can occur with non-dominant hemisphere lesions.

**31. Which of the following differentiates aphemia (pure word mutism) from Broca aphasia and transcortical motor aphasia?**

A. The ability to comprehend
B. The ability to repeat
C. The ability to write
D. The ability to do calculations

**32. Which of the following is a test of episodic memory that would best assess verbal and nonverbal memory in the visual domain?**

A. Peabody Picture Vocabulary Test
B. Rey–Osterrieth Complex Figure Test
C. Three Words–Three Shapes Test
D. Trail Making Test Part A
E. Trail Making Test Part B

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# BEHAVIORAL NEUROLOGY

## ANSWERS

**1. B**

Attention difficulties are characteristic of delirium. Patients with delirium are distractible and have difficulty performing goal-directed tasks. Working memory is impaired, and patients have difficulty with digit span testing.

Risk factors include advanced age, multiple medications, underlying medical and neurologic conditions, vision or auditory impairment, and sleep deprivation. Environmental conditions such as isolation and lack of daylight also contribute.

Medications are a common cause of delirium.

**2. D**

Triphasic waves are seen in the setting of metabolic encephalopathy.

Focal slowing indicates local dysfunction.

**3. A**

This patient has transient global amnesia (TGA), which is characterized by repetitive questioning and anterograde amnesia for several hours with normal findings on neurologic examination. Cognition is normal apart from the amnesia, and the patient remains oriented to self. Immediate memory and remote memories are intact, but there may be retrograde amnesia for the past weeks or years. Unlike patients with an acute confusional state, patients with TGA are able to maintain attention. Age older than 50 years is a risk factor. Some patients have a history of migraine. On magnetic resonance imaging (MRI), an abnormality in the hippocampus has been found in some patients.

Wernicke encephalopathy is less likely and is characterized by altered mental status, oculomotor abnormalities, and ataxia. It is due to thiamine deficiency and is associated with symmetric lesions of the mammillary bodies, periventricular regions of the hypothalamus and thalamus, periaqueductal gray, vestibular nuclei, and superior cerebellar vermis.

Patients with Wernicke encephalopathy who are not treated may develop Korsakoff syndrome, which is characterized by retrograde and anterograde amnesia with a tendency to confabulate. Patients with chronic symptoms have Wernicke–Korsakoff syndrome.

**4. True**

Although there are multiple techniques for determining hemispheric dominance for speech, memory is more difficult to assess. The Wada test (intracarotid sodium amobarbital test) is the gold standard for determining hemispheric dominance for speech and memory.

**5. A**

Motor impersistence, in which a patient has difficulty maintaining a motor task, may occur with nondominant frontal lobe lesions.

**6. B**

The patient has neglect of the left side, consistent with a right parietal lobe lesion. The patient also has asomatognosia (i.e., he denies ownership of a limb). This is usually caused by a contralateral parietal lobe lesion. The term *asomatognosia* may also be used when a patient lacks awareness of sensation from part of the body (e.g., due to posterior column or peripheral nerve disease).

The term *anosognosia* also applies in this case. This term refers to denial of deficits, which is typically a result of right parietal lesions. This denial may include denial of ownership of a limb.

*Anosodiaphoria* is the term for lack of concern about one's illness.

**7. A**

The frontal lobe is responsible for identification of problems, formulations of strategies, execution of plans, and evaluation of outcomes.

**8. A**

Episodic memory is most likely to be affected by normal aging. Episodic memory refers to memory of an event. Impaired episodic memory may cause patients to lose objects or ask questions repetitively.

**9. A**

Alzheimer disease (AD) is the most common cause of episodic memory impairment, and episodic memory is the core cognitive domain most likely to be affected by AD.[1] Normal episodic memory relies on the hippocampus and medial temporal lobe structures. Encoding, consolidation, and retrieval are involved in episodic memory.[2]

**10. A**

Semantic memory is declarative memory—knowledge of facts rather than memories about personal experience. It may manifest with anomia for words used infrequently.

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AD is the most common cause of semantic memory impairment and affects the inferolateral temporal lobes, which are critical for semantic memory.

**11. B**

Procedural memory refers to skills that are usually performed automatically, such as riding a bike. The supplementary motor area, cerebellum, and basal ganglia are crucial for procedural memory. Procedural memory is a type of nondeclarative memory.

**12. B**

Parkinson disease is the most common cause of impaired procedural memory.[2]

**13. A**

Working memory is an executive functioning skill that allows one to temporarily store and manipulate information—for instance, to perform calculations "in one's head." It allows short-term recall and is necessary for multitasking. The frontal lobe is primarily responsible.

**14. A**

Patients with memory deficits due to a frontal lobe lesion have impaired immediate memory, free recall, and recollection. Cued recall (recall after clues are given) and item memory tend to be normal. Patients may have false memories or confabulate. Environmental support improves memory performance.

Patients with medial temporal lobe lesions have impaired free recall, cued recall, recollection, and item memory. Environmental support is less likely to improve memory performance in these patients.

**15. B**

Lesions of the medial frontal lobe cause akinetic mutism, lower extremity weakness, and incontinence.

The orbitofrontal cortex is connected to the limbic system. Lesions of the orbitofrontal cortex cause disinhibition, impulsivity, and inappropriate jocularity (witzelsucht). Bilateral orbitofrontal lesions can cause imitation of gestures (echopraxia) and utilization behavior (manipulation of objects in the environment).

Perseveration is the tendency to repeat a behavior excessively. It is seen with certain frontal lobe lesions, including orbitofrontal lobe lesions. Also, motor perseveration can be seen with medial frontal lesions.

Lesions of the lateral frontal cortex cause apathy with intermittent bursts of anger/aggression. Patients have poor word list generation and psychomotor retardation.

**16. D**

Balint syndrome is characterized by the triad of simultagnosia, optic ataxia, and optic apraxia. In Balint syndrome, the patient has difficulty identifying moving objects.

Patients who can identify an object *only* when it is moving have visual static agnosia.

Balint syndrome occurs with bilateral parieto-occipital lesions. It is a type of disconnection syndrome. Other disconnection syndromes include alexia without agraphia, pure word deafness, and ideomotor apraxia.

**17. B**

A lesion of the left occipital lobe and adjacent corpus callosum causes alexia *without* agraphia. The patient may also have a right homonymous hemianopsia and difficulty naming colors.

Alexia *with* agraphia occurs with angular gyrus lesions in the dominant hemisphere.

Patients with pure word deafness (auditory verbal agnosia) have intact hearing but are unable to understand spoken language. Reading and writing are intact. Bilateral superior temporal gyrus lesions and certain dominant temporal lobe lesions can cause this.

Ideomotor apraxia is difficulty acting out an action when instructed to do so. There may be errors in hand–arm posture, joint movement, and target location.[2] When given an object with which to act out the action, the patient is better able to perform the task. This can occur with lesions to the dominant inferior parietal lobe, supplementary motor area, or frontal cortex and adjacent corpus callosum.

Patients with *ideational* apraxia have difficulty knowing which action to perform and have difficulty performing a series of actions in the correct sequence. There is a loss of plan for performing a task. Dominant parietal lobe lesions can cause this condition (Table 2.1).

*Table 2.1* NEUROANATOMY OF BEHAVIORAL NEUROLOGY CONDITIONS

| CONDITION | LESION(S) |
|---|---|
| **Alexia without agraphia** | **Left occipital region and adjacent corpus callosum** |
| **Balint syndrome** | **Bilateral parieto-occipital** |
| **Ideomotor apraxia** | **Dominant inferior parietal lobe, supplementary motor area, or frontal cortex and adjacent corpus callosum** |
| **Ideational apraxia** | **Dominant parietal lobe** |

Ideomotor apraxia and ideational apraxia are types of upper limb apraxia. Other types of upper limb apraxia include conceptual apraxia and limb-kinetic apraxia. Conceptual apraxia is associated with loss of mechanical knowledge, which may include not knowing which tool to use. Limb-kinetic apraxia refers to loss of dexterity/deftness. It can be assessed with the Coin Rotation Test and the Grooved Pegboard Test.[3]

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**18. A**

The condition described is Gerstmann syndrome. It is characterized by four primary symptoms: a writing disability (agraphia or dysgraphia), a lack of understanding of the rules for calculation or arithmetic (acalculia or dyscalculia), an inability to distinguish right from left, and an inability to identify fingers (finger agnosia). It is caused by a lesion in the dominant inferior parietal lobe.

**19. A**

Capgras syndrome is the term used when a patient believes his friends and family are duplicate imposters. It is a misidentification syndrome.

Cotard syndrome is characterized by nihilistic delusions regarding one's self or parts of one's body, including believing oneself to be dead.

Fregoli syndrome is another misidentification syndrome. It is the belief that a stranger is actually a friend in disguise.

Reduplicative paramnesia is the belief that locations have been duplicated.

Simultagnosia is the inability to see two objects at the same time. Only portions of the visual field are perceived, not the whole scene. This occurs in Balint syndrome.

**20. A**

Anton syndrome is the term for patients who deny their blindness. It can occur with bilateral posterior cerebral artery strokes.

A patient with impaired vision who has visual hallucinations has Charles Bonnet syndrome.

Patients with Ganser syndrome respond to questions with inaccurate, approximate answers.

Geschwind syndrome is a set of behavioral characteristics, such as hyperreligiosity, that was described in some patients with temporal lobe epilepsy. It has also been described in some patients with frontotemporal lobar degeneration.[4]

Bilateral anterior temporal lobe injury—for instance, due to Herpes simplex encephalitis—can cause Klüver–Bucy syndrome, which is associated with hyperorality, placidity, and hypersexuality.

**21. D**

*Prosopagnosia* is the term for difficulty recognizing faces. It is typically caused by bilateral occipitotemporal cortex (fusiform gyri) lesions. Achromatopsia (loss of color vision) can co-occur with prosopagnosia.

Prosopagnosia can be the presenting symptom of the semantic dementia variant of frontotemporal dementia.[5] It can also be seen in AD but is usually associated with visual–spatial deficits in those patients.

**22. A**

The Wisconsin Card Sorting Test, the Stroop Color and Word Test, and trail-making assess the frontal lobe.

The Stroop Color and Word Test evaluates attention and executive function, specifically response inhibition. During the task, the patient is asked to report the font color of a word when the word actually names a different color. For instance, if the word "yellow" is written in green ink, then the correct response is green.

The Wisconsin Card Sorting Test assesses executive functioning skills, including cognitive flexibility, problem–solving, and impulse control. During the task, the examinee is asked to sort cards by an unknown feature. The examiner indicates if the examinee has sorted the cards correctly. The objective is for the examinee to utilize the feedback of the examiner to discern the ways in which the cards are sorted—for instance, by color, shape, or number of figures on the card. During the task, the rule for sorting is changed without informing the examinee. Patients with frontal lobe injury continue to sort cards by the original sorting method despite feedback from the examiner that the choice is incorrect.

The Trail Making Test is a tool that is used to assess a person's visual scanning, mental sequencing, and mental flexibility to accurately connect dots according to the specified directions.

**23. A**

Go/no-go and sequencing tasks test the frontal lobe.

**24. A**

This patient's speech is not fluent, she comprehends, and she cannot repeat. This is Broca aphasia, which occurs with lesions of the dominant inferior frontal cortex, specifically the opercular and triangular parts of this gyrus.

If she could repeat, this would be transcortical motor aphasia, which is caused by a lesion anterior or superior to Broca's area. For instance, transcortical motor aphasia can occur with a stroke in the anterior cerebral artery (ACA) distribution or in the watershed area between the ACA and middle cerebral artery (MCA) territories.

**25. B**

This patient has Wernicke aphasia, which is caused by lesions of the dominant superior temporal gyrus. A visual field defect (homonymous hemianopia or quadrantanopia) may accompany Wernicke aphasia if the optic radiations are affected by the lesion. Anosognosia may also occur in patients with Wernicke aphasia.

**26. B**

This patient has conduction aphasia. Patients with conduction aphasia have fluent speech and are able to comprehend but cannot repeat. It can result from lesions in the insula, the posterior part of the superior temporal gyrus, or the supramarginal gyrus. Historically, it was thought to be caused by lesions of the arcuate fasciculus, which was thought to connect Broca's and Wernicke's areas; however, modern neuroimaging suggests that the connections between these areas are more complex.[6]

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Aphemia is a nonfluent aphasia.

Repetition is intact in transcortical aphasias.

**27. B**

This patient has a stroke in the left MCA territory. The lesion is at the stem of the MCA. A right homonymous hemianopsia is also seen with this lesion. A left gaze preference may be seen at the onset of symptoms.

A stroke in the territory of the superior division of the left MCA can cause Broca aphasia.

A stroke in the territory of the inferior division of the left MCA can cause Wernicke aphasia.

A lesion of the left ACA could cause weakness and sensory loss in the right leg and a transcortical motor aphasia.

**28. A**

This patient is most likely to have Broca aphasia. Broca's area is adjacent to primary motor cortex for the face, so a single lesion could cause Broca aphasia and facial weakness.

A stroke in the superior division of the left MCA could cause the clinical picture described in this case.

Transcortical sensory aphasia occurs with lesions near Wernicke's area.

Mixed transcortical aphasia can occur with strokes that affect the watershed region between the ACA and the MCA or the watershed region between the MCA and posterior cerebral artery in the dominant hemisphere—for instance, due to occlusion of the internal carotid artery. Mixed transcortical aphasia resembles global aphasia, but patients can repeat.

**29. C**

Anomic aphasia is more difficult to localize than other aphasias. Some cases are caused by lesions of the dominant angular gyrus. Anomic aphasia is characterized by word-finding difficulties, specifically difficulty naming. Otherwise, speech is fluent. Repetition and comprehension are intact. Anomia can occur in patients with AD or the semantic variant of primary progressive aphasia. It can also be seen in patients who are recovering from a more severe aphasia.

Lesions of the dominant angular gyrus can also cause Gerstmann syndrome and alexia.

Lesions to the dominant frontal operculum are more likely to cause Broca aphasia.

**30. True**

Expressive aprosodia can occur with nondominant hemisphere lesions. Nondominant frontal lobe lesions can be associated with monotone speech.

**31. C**

Aphemia is also referred to as pure word mutism. It is caused by small lesions in Broca's area or the adjacent subcortical white matter. Speech is difficult/effortful for patients with aphemia. However, comprehension, grammar, and writing are intact. Patients with Broca aphasia or transcortical motor aphasia are unable to write (Box 2.1).

### *Box 2.1* OVERVIEW OF THE APHASIAS

Fluent aphasias:
- Anomic
- Wernicke
- Conduction
- Transcortical sensory

Nonfluent aphasias:
- Global
- Broca
- Transcortical motor
- Mixed transcortical
- Aphemia

Problems with naming:
- Global
- Broca
- Wernicke
- Transcortical (motor, sensory, and mixed)
- Anomia
- Aphemia

Problems with repetition:
- Global
- Broca
- Wernicke
- Conduction
- Aphemia

Problems with comprehension:
- Global
- Wernicke
- Transcortical sensory
- Mixed transcortical

**32. C**

The Three Words–Three Shapes Test assesses verbal and nonverbal memory in the visual domain. It can be used to differentiate certain forms of primary progressive aphasia from amnestic dementia.[7]

The Peabody Picture Vocabulary Test assesses word comprehension/receptive vocabulary.

The Rey–Osterrieth Complex Figure Test assesses visual memory and visuospatial constructional ability.

The Trail Making Test Part A (all numbers) assesses attention and processing speed. Visual searching and motor skills are involved. The Trail Making Test Part B (numbers and letters) assesses task-switching as well.

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# 3.

# CEREBROVASCULAR DISEASE

## QUESTIONS

**1. A 79-year-old man with a history of hypertension, hyperlipidemia, and atrial fibrillation presents to the emergency department due to acute right-sided weakness in the face, arm, and leg with difficulty speaking. His symptoms started 1 hour prior to arrival. What is the first step in the triage process for this patient after initial stabilization?**

A. National Institute of Health (NIH) Stroke Scale assessment
B. Magnetic resonance imaging (MRI)
C. Administer recombinant tissue plasminogen activator (rtPA) or tenecteplase.
D. Transfer to a tertiary care center.

**2. The patient from Question 1 has a NIH Stroke Scale of 7, and the computed tomography (CT) scan of his head is negative for an acute hemorrhage. His blood pressure is 178/89 mm Hg. He has not taken his apixaban for atrial fibrillation in 3 days. What is the next step?**

A. MRI
B. CT perfusion
C. Administer rtPA or tenecteplase
D. Thrombectomy

**3. A 30-year-old pregnant woman in her third trimester starts to have a severe headache. The headache is associated with a left facial droop and left-sided weakness that started 6 hours prior to arrival. She tried Tylenol and hydration, but her symptoms are progressing. Her non-contrast CT of the head is negative. Which of the following is recommended first?**

A. Administer a migraine cocktail.
B. Administer rtPA or tenecteplase.
C. Order an MRI.
D. Order an MR venogram.

**4. The patient from Question 3 is found to have a cerebral venous thrombosis. In this case, what is the best next step?**

A. Aspirin
B. Warfarin
C. Heparin drip
D. Deliver the baby

**5. A 68-year-old woman with a history of morbid obesity, hypertension, and hyperlipidemia presents to the emergency department due to left third nerve palsy and ataxia in the right arm. Which of the following describes this syndrome?**

A. Weber syndrome
B. Benedikt syndrome
C. Claude syndrome
D. Parinaud syndrome

**6. A 75-year-old man with a history of hypertension, hyperlipidemia, and congestive heart failure with a reduced ejection fraction presents to the emergency department due to acute onset of right-sided hemiparesis and severe global aphasia. An acute stroke is suspected. What will the CT angiogram most likely show?**

A. Right middle cerebral artery (MCA) occlusion
B. Right anterior cerebral artery (ACA) occlusion
C. Left middle cerebral artery occlusion
D. Left anterior cerebral artery occlusion

**7. A 40-year-old man comes to the emergency department after suffering severe recurring headaches associated with aphasia and weakness. He admits to using cocaine while at a party the night prior. His brain MRI shows multiple small areas of acute infarction in the right frontal region. What is the most likely diagnosis?**

A. Cerebral vasospasm
B. Fibromuscular dysplasia (FMD)
C. Posterior reversible encephalopathy syndrome (PRES)
D. Complicated migraine

**8. A 28-year-old woman with no past medical history presents to the emergency department due to a 1-day history of persistent dizziness associated with nausea and ataxia. She states that she recently joined a yoga and Pilates program. Her exam is positive for nystagmus and right upper extremity dysmetria. What is the most likely diagnosis?**

A. Migraine with brainstem aura
B. Vertebral artery dissection
C. Cerebral venous sinus thrombosis
D. Ménière disease

**9. What is the most common inherited risk factor for thrombophilia?**

A. Protein S deficiency
B. Protein C deficiency
C. Factor V Leiden
D. Clotting cascade gene mutation

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**10. A 55-year-old woman presents to the emergency department due to 8 hours of acute-onset dizziness and confusion. A CT of the head shows a large cerebellar stroke with mass effect on the fourth ventricle. The patient is then seen to be more drowsy and less responsive. What would be the best next step?**

A. Digitally subtracted angiography
B. CT angiography
C. Consult Neurosurgery for a suboccipital decompression craniectomy.
D. Heparin drip

**11. A 7-year-old child is on a flight to Japan to visit her grandparents when she develops left arm weakness followed by a seizure. What is the most likely imaging finding?**

A. Multiple small arteries providing collateral circulation
B. Stenosis of the right posterior cerebral artery (PCA)
C. A patent foramen ovale (PFO)
D. Takotsubo-type cardiomyopathy on echocardiogram

**12. A 60-year-old man presents to the emergency department with ptosis of his right eyelid, dizziness, and decreased sensation to light touch on his left arm and leg. Which artery is most likely to be involved?**

A. Right posterior cerebral artery
B. Left posterior inferior cerebellar artery
C. Basilar artery
D. Right vertebral artery

**13. A 45-year-old man with a 30-year smoking pack-year history presents to the emergency department with an acute onset of severe paresthesias and numbness in the right arm and leg without any weakness or change in speech or vision. Where is the stroke most likely to be?**

A. Right basal ganglia
B. Right paramedian pontine distribution
C. Left anterior cerebral artery distribution
D. Left thalamus

**14. What is the mechanism of action of recombinant tissue plasminogen activator?**

A. Inhibits thrombin
B. Inhibits platelet aggregation
C. Converts plasminogen to plasmin and starts fibrinolysis
D. Competitively inhibits vitamin K epoxide reductase complex 1

**15. A 90-year-old man has a transient episode of aphasia and right arm weakness. His MRI of the brain is negative for acute stroke. Intracranial vessel imaging does not show any severe stenosis; however, his right extracranial internal carotid artery (ICA) shows 60% stenosis. The cervical segment of his left ICA has less than 50% stenosis. He is on aspirin. Which of the following is the best next step?**

A. Add clopidogrel for 90 days.
B. Refer him to a vascular surgeon for carotid endarterectomy (CEA).
C. Administer rtPA or tenecteplase.
D. No procedures are needed at this time.

**16. A 50-year-old female with a history of hypertension, diabetes, and obesity presents to the emergency department due to right facial droop and weakness affecting her right arm. There is no involvement of the right leg. She also has mild dysarthria but no change in vision or sensation. Where does the stroke localize?**

A. Left artery of Percheron
B. Right anterior cerebral artery
C. Right anterior choroidal artery
D. Left recurrent artery of Heubner

**17. A 78-year-old female presents with acute-onset somnolence, abnormal eye movements, and occasional agitation. A CT of the head was done, but no acute abnormality was seen. The patient remains obtunded for 24 hours, and the neurologist recommends an MRI. The MRI demonstrates bilateral thalamic infarcts. Which artery is responsible?**

A. Recurrent artery of Heubner
B. Artery of Percheron
C. Left PCA
D. Right anterior choroidal artery

**18. An 89-year-old male with a history of a prior stroke, hypertension, diabetes, and chronic tobacco use is being treated for a cryptogenic stroke. His echocardiogram with bubble study demonstrates a moderate-sized PFO. What are the next steps in his management?**

A. PFO closure
B. Transcranial Doppler
C. Consult interventional cardiology.
D. Start a cyclooxygenase inhibitor.

**19. What is the mechanism of action of clopidogrel?**

A. Inhibits platelet aggregation by disrupting the activation of the glycoprotein GPIIb/IIIa complex
B. Inhibits cyclooxygenase
C. Inhibits thrombin formation
D. Converts plasminogen to plasmin and starts fibrinolysis

**20. A 61-year-old male presents to the emergency department with a 5-hour history of left-sided hemiparesis that progresses to quadriplegia over 2 hours. His symptoms deteriorate, and he is now aphasic and only able to move his eyes. Where is the stroke?**

A. Top of the basilar artery
B. Bilateral thalami
C. Caudal pons
D. Bilateral ventral pons

**21. A 4-year-old boy with a history of abdominal pain and headaches has a sudden fall while he is playing. He is hemiplegic on the right side of his body. An MRI shows an acute right middle cerebral artery stroke. There is evidence of other small cortical lesions that look like chronic strokes. His lab studies are pertinent for anemia, and his echocardiogram is unremarkable.**

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**He was adopted at age 2 years, and there is no clear information about his biological parents. Which of the following tests is most likely to determine the etiology?**

A. Blood work looking for sickle cell disease
B. Digitally subtracted angiography
C. Transesophageal echocardiogram
D. Ultrasound of the lower extremities to look for deep vein thrombosis

**22. Which of the following accounts for the highest risk for stroke related to atrial fibrillation?**

A. Gender
B. History of congestive heart failure
C. Hypertension
D. History of prior stroke

**23. A 91-year-old woman with a history of dementia presents with altered mental status and then becomes obtunded. Her blood pressure is 130/75 mm Hg. The CT scan of her head shows a large lobar hemorrhage. What is the most likely etiology of her hemorrhage?**

A. Hypertensive bleed
B. Hemorrhagic conversion of an ischemic stroke
C. Cerebral amyloid angiopathy (CAA)
D. Trauma

**24. Which of the following is a contraindication to tPA/tenecteplase?**

A. Presenting within 3 hours of stroke symptom onset
B. Stroke that occurred 4 months prior
C. Seizure at onset of symptoms
D. International normalized ratio (INR) of 1.8 if currently on anticoagulation

**25. A 50-year-old left-handed patient presents to the emergency department due to confusion. She states she is having difficulty reading, but she has no trouble with writing. On exam, the patient is able to write a sentence but cannot read back what it says. She is also having difficulty with her visual field on the left side. Where do these deficits localize?**

A. Right MCA
B. Genu of the corpus callosum
C. Right PCA
D. Left vertebral artery

**26. A 38-year-old woman with a history of multiple spontaneous abortions presents to the emergency department with stroke-like symptoms. Which of the following tests is most likely to confirm her diagnosis?**

A. Testing for protein C deficiency
B. Testing for factor V Leiden
C. Testing for von Willebrand factor
D. Testing for antiphospholipid antibodies

**27. Which of the following is the gold standard test for central nervous system (CNS) vasculitis?**

A. Digitally subtracted angiography
B. CT angiography
C. Brain biopsy
D. Lumbar puncture

**28. A 75-year-old patient with a past medical history of hypertension and congestive heart failure, who lives independently and performs all her own activities of daily living, presents to the emergency department 7 hours after the onset of acute left-sided hemiparesis. A CT of the head shows a hyperdense MCA on the right side. CT angiogram shows a right M1 occlusion. CT perfusion shows a large penumbra. What is the best next step in management?**

A. Administer rtPA or tenecteplase.
B. Refer the patient to have emergent endovascular thrombectomy.
C. Start a heparin drip.
D. Administer aspirin 325 mg.

**29. Which of these patients would most benefit from CEA with an improved outcome compared to carotid artery stenting (CAS)?**

A. Patient with diabetes
B. Patient older than age 70 years
C. Patient on aspirin
D. Patient with peripheral vascular disease

**30. A 49-year-old patient with a history of a seizure disorder presents with right-sided hemiparesis. The patient's mother has a history of seizures, stroke, and dementia, and his older brother has a history of migraine with aura. Which genetic mutation is most likely?**

A. Mutation in the *NOTCH3* gene
B. Mutation in the *GLA* gene
C. Mutation in the *KRIT1* gene
D. Mutation in the *COL4A1* gene

**31. A 68-year-old man with a chronic history of tobacco use, chronic uncontrolled hypertension, and hyperlipidemia presents to the emergency department with dysarthria and right-sided weakness. His MRI shows an acute stroke in the watershed area between the left ACA and MCA. Which of the following imaging findings is most likely?**

A. A PFO on his echocardiogram
B. Cardiac thrombus on cardiac echo
C. High-grade stenosis in the left ICA
D. High-grade stenosis of the left M1

**32. An 80-year-old female presents to the emergency department with dense left-sided hemiplegia and a forced gaze to the right that started 2 hours prior to arrival. Her CT has an Alberta Stroke Program Early CT Score (ASPECTS) score of 10, and CT angiogram demonstrates a left ICA occlusion blocking the proximal M1. At baseline, this patient is very active. She lives by herself and walks 2 miles daily without the need for a walker or cane. What is the best next step?**

A. Administer rtPA or tenecteplase.
B. Start a heparin drip.

C. Administer rtPA or tenecteplase and refer her for endovascular mechanical thrombectomy.
D. Take the patient directly to thrombectomy.

33. **Which of the following is true regarding the anatomy of the cervicovertebral arterial circulation?**
A. The common carotid artery typically divides into the internal and external carotid arteries at the level of C7.
B. The right vertebral artery originates from the right subclavian artery.
C. The left ICA originates from the aorta.
D. The left vertebral artery originates from the innominate (brachiocephalic) artery.

34. **A 55-year-old woman with a history of hypertension and chronic tobacco use presents to the emergency department due to acute vision change and tremor. Her left eye appears to be in the inferolateral position, and the pupil is dilated. On dysmetria testing, she is seen to have an intention tremor and difficulty controlling her right arm. Where is the stroke?**
A. Left lateral medulla
B. Left ventral midbrain
C. Right superior cerebellar peduncle
D. Right medial midbrain

35. **A 49-year-old man presents to the emergency department due to left-sided hemiparesis with ataxia and right cranial nerve III (CN 3) palsy. Where is his stroke localized to?**
A. Right medial midbrain
B. Right ventral midbrain
C. Medial medulla
D. Left lateral medulla

36. **A 60-year-old woman presents to the emergency department with acute visual changes. On examination of horizontal eye movements, she can only abduct her left eye, which demonstrates nystagmus when abducted. What artery is responsible for these findings?**
A. Right vertebral artery
B. Left paramedian pontine perforators
C. Deep penetrating artery from the PCA
D. Right paramedian pontine perforators

37. **A 38-year-old woman was getting her hair cut and dyed at the salon. She started to feel nauseated while getting her hair washed. When she stood up, she was dizzy, her right eyelid was drooping, the right side of her face and the left side of her body had decreased pain sensation, and she had right arm ataxia. She is taken to the emergency department, where the physician suspects she has suffered an arterial dissection. What is the best test to diagnose this?**
A. MR angiography (MRA) of the circle of Willis
B. Catheter angiogram of the cervicovertebral arteries
C. Carotid ultrasound
D. Transthoracic echo with bubble study

38. **A 50-year-old man presents to the emergency department obtunded. A stat CT of the head shows significant subarachnoid bleeding. A CT angiogram demonstrates an aneurysm. What is the most likely location of the saccular berry aneurysm?**
A. Basilar artery
B. The bifurcation of the internal and common carotid artery
C. The bifurcation of the ICA and MCA
D. The origin of the posterior inferior cerebellar artery from the vertebral artery

39. **A 45-year-old man with a history of selective serotonin reuptake inhibitor (SSRI) use due to depression and polysubstance use presents with sudden-onset headache that peaks within 1 second and then starts to resolve in a few hours. He has no focal deficits on exam but endorses nausea, vomiting, photophobia, and phonophobia. A CT of the patient's head shows a small subarachnoid hemorrhage. The patient's CT angiogram shows beading of the MCA and ACA. The patient's headache improves, and he is symptom-free when he is seen in follow-up 3 months later. What is true about this condition?**
A. Steroids are the gold standard treatment.
B. Brain biopsy should be done to establish a diagnosis.
C. This condition does not cause ischemic strokes.
D. Repeat CT angiography usually shows resolution by 12 weeks.

40. **Which of the following is *not* usually a symptom seen in medial medullary syndrome?**
A. Ipsilateral tongue weakness
B. Contralesional loss of vibration
C. Contralesional facial droop
D. Contralesional limb weakness

41. **What is the mechanism of action of rivaroxaban?**
A. It is a factor Xa inhibitor.
B. It inhibits platelet aggregation.
C. It is a thrombin inhibitor.
D. It antagonizes the vitamin K–dependent clotting pathway.

42. **Which area on a CT scan is *not* considered in the ASPECTS score?**
A. Internal capsule
B. Caudate head
C. Insular cortex
D. Thalamus

43. **A 65-year-old woman with a history of hypertension and hyperlipidemia presents to the emergency department due to acute, painless vision loss in her right eye that started 4 hours prior to arrival. The patient is evaluated with a CT of the head, which is negative. CT angiogram shows 80% stenosis of the right ICA. Her MRI is negative for acute stroke, but her dilated fundoscopy demonstrates a cherry-red spot. What is the likely etiology of her symptoms?**

A. Cholesterol embolism from her heart
B. A platelet fibrin embolism to the ophthalmic artery
C. A platelet fibrin embolism to her calcarine cortex
D. A calcium embolism from her ICA to the dorsal nasal artery

**44. Which one of these parameters is *not* used to calculate the ABCD2 transient ischemic attack (TIA) score?**
A. Age
B. Gender
C. Diabetes
D. Hypertension

**45. Which of the following is least likely to be present if a patient has a dissection of the ICA?**
A. Anhidrosis
B. Ptosis
C. Miosis
D. Headache

**46. A stroke in which of these territories causes the lateral pontine syndrome (ipsilateral facial paralysis, unilateral deafness, vertigo, facial hemianesthesia, contralateral loss of pain and temperature, ataxia, and ipsilateral Horner syndrome)?**
A. Anterior inferior cerebellar artery (AICA)
B. Anterior spinal artery
C. Paramedian branches of the basilar artery
D. Posterior inferior cerebellar artery (PICA)

**47. Which of the following is least likely to be due to a lacunar stroke in a left hemisphere dominant person?**
A. Left-sided weakness involving the face, arm, and leg
B. Left-sided numbness involving the face, arm, and leg
C. Dysarthria and a clumsy left arm
D. Left face and arm weakness and left hemineglect

**48. A 20-year-old man with a history of intellectual disability and myopia presents with stroke. On examination, he is tall and thin. Serum and urine amino acids confirm his diagnosis. A trial of which medication is recommended to treat the underlying condition?**
A. Carnitine
B. Coenzyme Q10
C. Pyridoxine
D. Warfarin

**49. In a patient with sickle cell disease and high-velocity flow in the MCA demonstrated on transcranial Doppler ultrasonography, which of the following is the best method to prevent stroke?**
A. Avoid iron deficiency anemia.
B. Transfuse the patient to maintain a hemoglobin S concentration at less than 30% of the total hemoglobin concentration.
C. Transfuse the patient when symptoms occur.
D. Transfuse the patient if symptoms persist after hydration.

**50. A 16-year-old presents with a seizure and is found to have an aneurysm. On review of systems, the mother mentions academic difficulties and nose bleeds. There is a family history of arteriovenous malformation and hearing loss. The mother has telangiectasias on her face. A defect in the gene encoding which of the following proteins needs to be considered?**
A. Endoglin
B. Tuberin
C. Hamartin
D. Merlin

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# CEREBROVASCULAR DISEASE

## ANSWERS

### 1. A

The first step in triaging a stroke patient is getting a rapid assessment. First check the patient's ABCs—airway, breathing, and circulation. After initial stabilization, an NIH Stroke Scale assessment will determine the severity of the symptoms of the suspected stroke. The patient should have head and brain imaging done, usually with CT or MRI. (See Box 3.1 for early signs of ischemia on CT.) When determining if a patient is a candidate for rtPA, it is important to look at the exclusion criteria and the brain imaging to limit any potential side effects from the thrombolytic.[1]

#### *Box 3.1* EARLY SIGNS OF ISCHEMIA ON COMPUTED TOMOGRAPHY

- Loss of gray–white differentiation
  - Lenticular obscuration
  - Cortical ribbon sign
  - Insular ribbon sign
- Sulcal effacement
- Hyperdense MCA or MCA dot sign

### 2. C

Recombinant tissue plasminogen activator (rtPA) is a thrombolytic that is used in the acute treatment of ischemic stroke. This patient meets the inclusion criteria for rtPA administration and does not have any of the exclusion criteria.

The earlier the administration of rtPA after the stroke symptom onset, the lower the chances are of hemorrhagic complications. According to the 1995 National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study, patients with acute stroke who received intravenous rtPA within 3 hours of onset of stroke symptoms had improved clinical outcomes with lower rates of disability at 3 months.[2] There are specific inclusion and exclusion criteria for rtPA to ensure patients receiving this treatment are appropriate candidates. Initial inclusion criteria for administering rtPA for acute ischemic stroke included age 18 years or older, diagnosis of ischemic stroke causing a neurological deficit, and onset of symptoms less than 3 hours before treatment is initiated.[3] It is also important that this patient does not meet any of the exclusion criteria.

Some of the early exclusion criteria for administering rtPA for acute ischemic stroke included significant head trauma or prior stroke within the previous 3 months; suspected subarachnoid hemorrhage; arterial puncture at a noncompressible site in the previous 7 days; previous intracranial hemorrhage; intracranial tumor, arteriovenous malformation, or aneurysm; recent intracranial or intraspinal surgery; elevated blood pressure (systolic >185 mm Hg or diastolic >110 mm Hg); active internal bleeding or acute bleeding diathesis; blood glucose concentration <50 mg/dL; or multilobar infarction on CT.[3] Relative contraindications to tPA included pregnancy, seizure at onset with postictal residual neurological impairments, major surgery or serious trauma within the previous 14 days, gastrointestinal or urinary tract hemorrhage within 21 days, acute myocardial infarction within the previous 3 months, and having only minor symptoms.[3]

The Third European Cooperative Acute Stroke Study (ECASS 3) evaluated using rtPA for acute ischemic stroke with symptom onset between 3 and 4.5 hours. This study demonstrated that for select patients, there is benefit in morbidity and mortality to administering rtPA to patients with stroke symptoms that started between 3 and 4.5 hours prior. For this specific time window of 3 to 4.5 hours after onset of stroke symptoms, there are additional exclusion criteria to consider before administration, including National Institutes of Health Stroke Scale (NIHSS) >25, age older than 80 years, history of stroke and diabetes, and any anticoagulation use regardless of INR or partial thromboplastin time. (See Box 3.2.) These factors increase the risk of hemorrhage after the administration of tPA during this time window.[3]

#### *Box 3.2* EXCLUSION CRITERIA FOR ADMINISTRATION OF RTPA BETWEEN 3 AND 4.5 HOURS AFTER THE ONSET OF A STROKE

- Age >80 years
- Patient is taking anticoagulants (regardless of the international normalized ratio)
- NIHSS score greater than 25
- Ischemic injury involves more than one-third of the MCA territory
- History of both stroke and diabetes mellitus

Tenecteplase is a genetically engineered form of tPA. It is a thrombolytic medication that is used to treat acute stroke. It can be administered in lieu of tPA and has the same exclusion and inclusion criteria.[4] Tenecteplase has more fibrin specificity than alteplase.[4]

MRI is not necessary to make a decision about administering rtPA. CT perfusion is not necessary in determining if a patient is a candidate for rtPA. It can take time for this study to be completed, and it requires a clinician to interpret the scan.[5]

**3. D**

There is an increased risk of venous thrombosis in the brain and in other parts of the body during pregnancy and puerperium. Cerebral venous thrombosis accounts for up to 57% of pregnancy-related strokes.[6] MRI with MR venogram is considered the gold standard for diagnosing a cerebral venous thrombosis. Misdiagnosing a cerebral venous thrombosis can have potentially fatal outcomes.[6,7]

**4. C**

The treatment of a cerebral venous thrombosis includes anticoagulation and, in some cases, surgical thrombectomy. During pregnancy, warfarin should be avoided because it can cause bleeding complications. Warfarin is a category D medication for complications during pregnancy. Low-molecular-weight heparin would be the treatment of choice as an outpatient. Low-molecular-weight heparin and unfractionated heparin do not cross the placenta. A heparin drip is the treatment of choice in the acute inpatient setting. According to the RE-SPECT CVT prospective randomized multicenter clinical trial, in a nonpregnant patient, dabigatran and warfarin were both found to have low risk of recurrent cerebral venous thrombosis and are safe and effective for preventing recurrent cerebral venous thrombosis.[6,8]

**5. C**

This case describes Claude syndrome, which is due to a midbrain tegmental lesion. The third nerve, brachium conjunctivum, and red nucleus are involved. The patient has a CN 3 palsy ipsilateral to the lesion and ataxia in the limbs contralateral to the lesion.

Benedikt syndrome is discussed in Question 34.

Parinaud syndrome is caused by injury to the dorsal midbrain and quadrigeminal plate. This syndrome is often seen when there is compression of the superior colliculus. There is impaired upward gaze, light-near dissociation, and convergence–retraction nystagmus. This can be caused by any process that damages the dorsal midbrain, including stroke, hemorrhage, or tumors. This syndrome is often seen in tumors of the pineal gland.

Weber syndrome is caused by an injury to the medial midbrain. The ipsilateral third cranial nerve is involved, and involvement of the cerebral peduncle causes contralateral hemiplegia.[9]

**6. C**

This patient is presenting with acute left MCA syndrome, likely affecting the M1 branch of the MCA given the patient's global aphasia. In the majority of patients, the left cerebral hemisphere controls the majority of a person's language ability despite handedness. The superior branch of the MCA on the left side supplies Broca's area, which is responsible for the motor aspect of language production. The inferior branch of the MCA supplies Wernicke's area, which is important for language comprehension. For a stroke to cause global aphasia, which is characterized by inability to produce or comprehend language or to repeat, a blockage of the MCA must occur before that artery bifurcates. Thus, a proximal M1 occlusion would be responsible. This type of stroke would typically result in a large area of infarction that could result in weakness and sensory changes in the contralateral face, arm, and leg as well.[9]

**7. A**

Cocaine is a CNS sympathomimetic drug. It inhibits the reuptake of neurotransmitters such as norepinephrine, dopamine, and serotonin at presynaptic nerve terminals. Increased levels of norepinephrine and serotonin can cause vasospasm. This process significantly increases the risk of ischemic and hemorrhagic stroke.[10]

Fibromuscular dysplasia (FMD) is a vascular disorder that affects the small and medium arteries, resulting in aneurysms, occlusions, stenosis, and dissection. This disorder most commonly affects the renal arteries, extracranial carotid arteries, and vertebral arteries. The vessels affected can look like a string of beads due to alternating stenosis and dilation. The most common clinical manifestations of FMD include hypertension (due to the effect on the renal arteries), headaches, pulsatile tinnitus, dizziness, TIA, and stroke due to arterial dissection. This process is not caused by inflammation or atherosclerosis. There is a predominance in women compared to men.[11]

Posterior reversible encephalopathy syndrome (PRES) usually presents with altered mental status, seizures, headache, and sometimes visual impairment often in the setting of elevated blood pressure. T1- and T2-weighted MRI images will typically show symmetric hyperintensities in the posterior aspect of the cerebrum; however, PRES can also affect other parts of the brain.

**8. B**

This patient is experiencing a vertebral artery dissection. Hyperextension of the neck, blunt trauma, torsion, and manipulation of the neck have all been documented as reasons for cervical arterial dissection. Given that this patient is a participant in a yoga and Pilates program, she is likely doing exercises that can cause hyperextension of the neck and injury if not done correctly. Common signs and symptoms of vertebral artery dissection include headache, dizziness, nausea, ptosis, and disequilibrium. The most common site of vertebral dissection is at the C1–C2 level, where the vertebral artery leaves the transverse foramina to enter the cranium. The artery is very mobile at this point, which can cause a dissection and

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then a stroke of the cerebellum or medulla. The gold standard method to diagnose and follow this condition is with digitally subtracted angiography. CT angiography and MRA are also beneficial studies to diagnose dissection. MR with fat saturation has also been used.[12]

Migraine with brainstem aura typically occurs in people who have a history of migraine and aura. These patients can also experience transient dysarthria, aphasia, diplopia, vertigo, tinnitus, and ataxia.

Cerebral venous sinus thrombosis does not typically present with these symptoms. This patient does not have risk factors associated with cerebral venous sinus thrombosis.[7]

Ménière disease is a disorder of the inner ear that results in hearing loss and dizziness.[9]

**9. C**

Factor V Leiden is the most common inherited risk factor for thrombophilia.[13]

Factor V is involved in the formation of fibrin, which is needed for clot formation. In a person without this disorder, activated protein C inactivates factor V. Patients with factor V Leiden are resistant to activated protein C; therefore, clotting continues. Patients with factor V Leiden are at risk for venous thromboembolism, especially in the deep veins.

**10. C**

Improved survival has been found in patients with cerebellar stroke with a volume ratio between 0.25 and 0.33 who are able to get a preventative suboccipital decompression within 72 hours of stroke onset. This was based on a retrospective-matched case–control study that compared preventative suboccipital decompression craniectomy to best medical management alone.[14]

None of the other options would lead to improved morbidity or mortality of this patient.

**11. A**

Based on the history, this patient likely has moyamoya disease. *Moyamoya* means "puff of smoke" in Japanese. The incidence of this condition is higher in Asian countries. The history alludes to this patient's Japanese ancestry, and her symptoms of weakness and seizure are commonly found in patients with moyamoya disease. In this condition, the carotid artery is significantly stenosed or occluded, so over time a network of small collateral arteries form to supply the brain with blood. This network of collateral arteries gives the appearance of a puff of smoke on angiogram. Stroke, TIA, seizure, headaches, vision changes, and cognitive delays can all be seen in patients with moyamoya disease.[15]

**12. D**

This is Wallenberg syndrome or lateral medullary syndrome. It is most often caused by an occlusion of the vertebral artery or PICA. Patients with Wallenberg syndrome can experience vertigo due to the involvement of the vestibular nuclei; decreased pain and temperature in the ipsilateral face due to the involvement of the trigeminal nucleus; loss of pain and temperature sensation in the contralateral body due to the involvement of the spinothalamic tract; ipsilateral Horner syndrome due to the involvement of descending sympathetic fibers; ipsilateral ataxia due to involvement of the cerebellar peduncle; hoarseness and dysphagia due to involvement of the nucleus ambiguous; and decreased taste due to involvement of the nucleus solitarius.[9] See Figure 3.1.

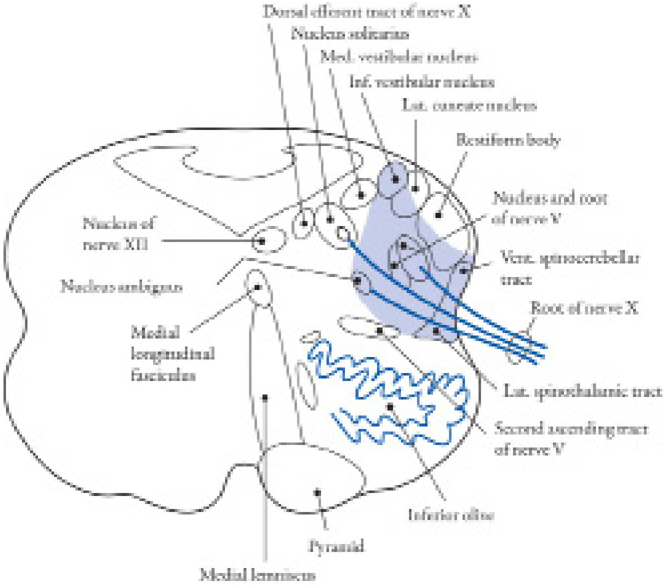

**Figure 3.1** Cross-section of the medulla illustrating the zone of infarction with Wallenberg syndrome. Inf., inferior; Lat., lateral; Med., medial; Vent., ventral. SOURCE: From Baloh RW, Honrubia V, Kerber K, eds. *Baloh and Honrubia's Clinical Neurophysiology of the Vestibular System*, 4th ed., Fig. 14-1. New York: Oxford University Press; 2011.

**13. D**

This patient is experiencing one of the lacunar syndromes, which include the following: pure motor symptoms, pure sensory symptoms, sensorimotor symptoms, dysarthria–clumsy hand syndrome, hemiparesis with ataxia, and hemiballismus.

- Pure motor symptoms: The stroke causes contralateral hemiparesis usually due to infarct of the internal capsule (posterior limb), corona radiata, or basis pontis.
- Pure sensory symptoms: The stroke causes contralateral hemisensory changes without motor weakness due to an infarct of the thalamus (ventroposterolateral nucleus).
- Sensorimotor symptoms: The stroke causes hemisensory and motor changes due to injury of the internal capsule with adjacent injury to the thalamus.
- Dysarthria–clumsy hand syndrome: The stroke causes slurred speech, dysphagia, and decreased

dexterity of the contralateral hand due to an infarct of the basis pontis or internal capsule.

- Hemiparesis with ataxia: The stroke causes hemiparesis and ataxia in the contralateral limbs due to an infarct of the internal capsule or basis pontis.
- Hemiballismus: The stroke causes contralateral hemiballismus due to a lesion of the subthalamic nucleus.[9]

**14. C**

Recombinant tissue plasminogen activator and tenecteplase convert plasminogen to plasmin, which initiates fibrinolysis.

**15. D**

This patient has suffered a TIA. There is no evidence of acute ischemic injury on his MRI. His right ICA is considered to have moderate carotid stenosis, which is defined as 50–69% by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria. This artery, however, is not the one responsible for the patient's symptoms. His left ICA is considered to have mild stenosis by the NASCET criteria, <50%.[16] Given the negative brain imaging and mild stenosis of the left ICA, no acute vascular intervention needs to be done at this time. Aspirin and clopidogrel for 90 days were a part of the recommendation made by the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial. The combination of aspirin 325 mg daily and clopidogrel 75 mg daily for 90 days with intensive risk factor management was recommended for patients with TIA/cerebrovascular accident due to 70–99% intracranial arterial stenosis, which is not what is seen on this patient's imaging.[17]

**16. D**

This patient has a stroke in the area of the brain supplied by the recurrent artery of Heubner. The recurrent artery of Heubner is a branch of the ACA. It supplies the caudate head, anterior limb of the internal capsule, and anterior putamen. A stroke affecting this artery results in contralateral face and arm weakness but typically spares the leg. Dysarthria can also be seen in patients with this type of stroke.

**17. B**

The artery of Percheron is a rare vascular variant. It is a vessel that branches off the P1 segment of either the left or right PCA and supplies the paramedian thalami bilaterally and the rostral midbrain. A stroke affecting the artery of Percheron would cause bilateral thalamic infarcts, which can result in vertical gaze palsy, agitation, cognitive changes, and coma.

ACA strokes typically result in contralateral leg weakness that is more severe than arm weakness, with or without sensory changes. There can also be loss of voluntary micturition.

The anterior choroidal artery originates from the posterior aspect of the ICA distal to the posterior communicating artery. It supplies the globus pallidus interna, part of the posterior limb of the internal capsule, part of the geniculocalcarine tract, the choroid plexus, the uncus, the amygdala, the anterior hippocampus, the optic tract, and the lateral geniculate nucleus. A stroke affecting the structures supplied by the anterior choroidal artery can result in hemiplegia, hemisensory loss due to thalamic involvement, and homonymous hemianopia.[9] Involvement of the lateral geniculate body can sometimes cause a sectoranopia with sparing in the horizontal meridian.

**18. D**

In this patient, calculating the Risk of Paradoxical Embolism (RoPE) score will help determine the management. This score takes into account risk factors such as hypertension, history of diabetes, history of stroke or TIA, smoking history, the appearance of cortical stroke on imaging, and age. Higher scores indicate that there is a higher likelihood that the patient's stroke is due to a paradoxical embolism. A score of 0 is assigned if the patient has a history of hypertension, diabetes, or stroke and if they are a smoker. One point is assigned if there is a cortical infarct seen on the imaging. With his age of 89 years, this patient would have a RoPE score of 1, which indicates a 0% chance that his stroke is due to a paradoxical embolism via the PFO.[18] This patient would be best treated with aspirin, which is a cyclooxygenase inhibitor.

**19. A**

Clopidogrel inhibits platelet aggregation. Specifically, clopidogrel is an adenosine diphosphate (ADP) P2Y12 receptor antagonist; it prevents ADP from binding the P2Y12 receptor on the platelet. This prevents ADP-mediated activation of glycoprotein IIb/IIIa, which is necessary for platelet aggregation.

Aspirin is a medication that causes acetylation of cycloogenoxidase-1 and cycloogenoxidase-2 in platelets, which inhibits the synthesis of thromboxane $A_2$ and thus inhibits platelet aggregation.[19,20]

Thrombin converts soluble fibrinogen to insoluble fibrin and also stimulates platelet activation. Direct thrombin inhibitors inactivate free thrombin and thrombin that is bound to fibrin, which prevents clot formation. Direct thrombin inhibitors include medications such as dabigatran, bivalirudin, lepirudin, and argatroban. Indirect thrombin inhibitors include unfractionated heparin and low-molecular-weight heparin.

tPA (endogenous and exogenous) converts plasminogen to plasmin, which starts the process of fibrinolysis.[19,20]

**20. D**

This patient is experiencing locked-in syndrome due to a stroke of the ventral pons. In this condition, the patient is awake and conscious but quadriplegic with paralysis of certain cranial nerves. Most patients are not able to speak and have a horizontal gaze palsy. Because the vertical gaze centers of the brain are spared, these patients are able to move their eyes up and down, and the ability to blink is preserved. Patients with this condition might be able to communicate with the vertical movement of their eyes and blinking.[9]

The top of the basilar artery supplies the rostral brainstem. In top of the basilar syndrome, patients can experience visual and oculomotor changes. There can also be hallucinations, behavior changes, and somnolence. Regions of the brain supplied by the proximal posterior cerebral arteries can also be affected by stroke of the distal basilar artery. This includes structures such as the thalamus.

A stroke affecting bilateral thalami is caused by a lesion to the artery of Percheron. The symptoms are typically vertical gaze palsy, agitation, cognitive changes, and coma.

A lesion of the caudal pons can lead to symptoms consistent with Millard–Gubler syndrome, Foville syndrome, or Raymond syndrome. Millard–Gubler syndrome symptoms include ipsilateral CN 6 and 7 palsy (peripheral facial weakness) with contralateral hemiparesis. Foville syndrome symptoms include ipsilateral facial weakness (peripheral), weakness of conjugate gaze to the side of the lesion (due to paramedian pontine reticular formation [PPRF] involvement), and contralateral hemiparesis. Raymond syndrome symptoms are contralateral hemiparesis and CN 6 palsy without the involvement of CN 7.[9]

**21. A**

This boy has been experiencing abdominal pain and headaches, which can occur due to sickle cell anemia. He was adopted, so his family history is not clear. The other cortical lesions seen on MRI represent silent strokes that can occur in children who have sickle cell anemia. Sickle cell poses a high risk for stroke due to the abnormal shape of the red blood cells, which can easily aggregate.[9]

**22. D**

Atrial fibrillation is an abnormal heart rhythm that significantly increases the risk of stroke. The CHA2DS2–VASc score has been used to estimate the stroke risk of patients who have atrial fibrillation. CHA2DS2–VASc is an acronym for the risk factors that get assigned points. Higher scores indicate a greater risk of stroke due to atrial fibrillation. In scoring the risk factors, the only two risk factors that are worth 2 points instead of 1 are age 75 years or older and history of previous stroke or TIA. The maximum score is 9. (See Box 3.3.)

### *Box 3.3* CHA2DS2–VASC

The $CHA_2DS_2$–VASc score estimates the risk for stroke in a patient with atrial fibrillation. It provides a better stratification of low-risk patients than the $CHADS_2$ score. The acronym $CHA_2DS_2$-VASc stands for

- Congestive heart failure
- Hypertension
- Age ≥75 years
- Diabetes mellitus
- Stroke or TIA previously
- Vascular disease
- Age 65–74 years
- Sex category (i.e., female sex)

In scoring, age ≥75 years or a previous stroke or TIA gives 2 points; age 65–74 years and the others give 1 point each. The maximum score is 9.

The risk for bleeding from anticoagulation in a patient with atrial fibrillation is determined by the HAS–BLED score (see Box 3.4).

### *Box 3.4* HAS–BLED

The HAS–BLED score is used to determine the 1-year risk for major bleeding from anticoagulation in a patient with atrial fibrillation. The acronym HAS-BLED stands for

- Hypertension
- Abnormal liver or renal function
- Stroke
- Bleeding previously or predisposition to bleeding
- Labile INR
- Elderly (age >65 years)
- Drug or alcohol use

Vitamin K antagonists (e.g., warfarin), apixaban, or dabigatran can be used to prevent recurrent stroke or TIA in patients with nonvalvular atrial fibrillation. Rivaroxaban can also be used.

In many patients who have atrial fibrillation and have had a stroke, oral anticoagulation can be started within 2 weeks of the stroke. However, if there is a high risk of hemorrhagic conversion, delaying the initiation of treatment is recommended.

**23. C**

Given this patient's blood pressure at presentation, which is not significantly elevated, her history of dementia, and the lobar location of the hemorrhage, the etiology of the intracerebral hemorrhage is most likely to be cerebral amyloid angiopathy (CAA). CAA is a form of

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small-vessel disease caused by β-amyloid deposition in the walls of cortical arteries, capillaries, and leptomeningeal arteries. Common clinical manifestations of CAA include intracerebral hemorrhage (and recurrent hemorrhages) in a lobar distribution, as well as decline in cognition. There is a high co-occurrence of Alzheimer disease and pathologies associated with CAA.[21] MRI with gradient echo will demonstrate multiple small hypointense areas in the cortex indicating prior hemosiderin deposition. Histologically, there is deposition of amyloid in the media and adventitia of the small and medium-sized blood vessels, which can be visualized using Congo Red.[21] Familial CAA, which is caused by mutations in *APP*, leads to white matter abnormalities, as well as lobar hemorrhage and microbleeds.

Hypertensive intracerebral hemorrhages are usually located in the basal ganglia, thalamus, pons, and cerebellum. These hemorrhages are not typically located in the cortex. The patient usually presents with an elevated blood pressure and may or may not have a history of hypertension.

Hemorrhagic conversion of ischemic strokes will often have changes in diffusion-weighted imaging associated with the positive gradient echo on MRI. This represents dysfunction of $Na^+/K^+$-ATPase, which is what causes cytotoxic edema. This imaging finding is not seen in CAA.

Trauma can cause intracerebral hemorrhage such as subdural hematomas, coup contrecoup injury, epidural hematoma, subarachnoid hemorrhage, as well as intraparenchymal hemorrhage. A history of trauma is important in determining the etiology of the hemorrhage.

**24. D**

See the answer for Question 2 for more information.

**25. C**

The cortical branches of the PCA supply the posterior medial parietal lobe, the splenium of the corpus callosum, the inferior and medial parts of the temporal lobe, the hippocampal formation, and the medial and inferior surfaces of the occipital lobe. This patient is experiencing alexia without agraphia, which is a phenomenon seen when a patient has a stroke affecting the splenium of the corpus callosum. Alexia without agraphia means a patient is unable to read, but their ability to write is unaffected. In addition, because the PCA supplies the occipital lobe, this patient is also experiencing a contralateral visual field deficit.[9]

**26. D**

Antiphospholipid syndrome is characterized by arterial and venous thromboses and miscarriages caused by circulating antiphospholipid antibodies. Due to arterial and venous thromboses, patients have a high risk for ischemic stroke.

Protein C regulates the activity of factors VIIIa and Va. Activated protein C with the cofactor protein S inhibit coagulation by deactivating factors VIIIa and Va on the surface of the phospholipid membrane. Protein C deficiency is a genetic defect that can lead to systemic venous thrombosis.

Patients with factor V Leiden are resistant to activated protein C, so clotting continues.

Von Willebrand disease is the most common bleeding disorder. In this condition, the lack of Von Willebrand factor results in decreased clotting ability. Symptoms of Von Willebrand disease include easy bruising, frequent nosebleeds, bleeding gums, prolonged bleeding from cuts, and heavy menses.

**27. C**

Primary CNS vasculitis or primary angiitis of the CNS is an inflammatory disorder that affects the blood vessels of the CNS. The classic symptoms associated with this condition include headache, seizures, ischemia, and, rarely, hemorrhage. The gold standard test for diagnosing this condition remains a brain biopsy.[9] Digitally subtracted angiography is also an excellent tool in diagnosing this condition; however, this test might not visualize changes to very small vessels. CT angiogram and lumbar puncture are also used in the initial evaluation of this condition; however, a brain biopsy is the mainstay for diagnosis.

**28. B**

This patient should have emergent endovascular thrombectomy.

In 2017, the DAWN and DEFUSE 3 trials extended the time window for the appropriate candidates to have endovascular thrombectomy for an occlusion causing a stroke, involving the ICA and/or the first segment of the MCA, up to 24 hours.[22–24] This patient meets the age criteria, functional status criteria—modified Rankin score of ≤2, last well-known time within 24 hours, and absence of intracerebral hemorrhage. This patient should not be administered rtPA or tenecteplase because the symptom onset started 7 hours prior to arrival. Heparin drip and acetylsalicylic acid 325 mg are not the standard of care for a patient who meets the criteria for endovascular mechanical thrombectomy.[22,23]

**29. B**

In patients older than age 70 years, CEA has a lower risk of recurrent stroke or death within 30 days of treatment. There is a higher periprocedural stroke risk in patients older than age 70 years undergoing CAS. CAS and CEA are equivalent in preventing recurring stroke 30 days after the procedure.[25]

**30. A**

This patient has cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy (CADASIL). Patients with CADASIL can experience migraine with aura, strokes, seizures, cognitive impairment, and early dementia. Because it is autosomal dominant, family members will often experience one or more of the conditions caused by CADASIL. CADASIL is most commonly caused by a missense mutation of the *NOTCH3* gene on chromosome 19. If gene testing is negative, a skin biopsy can be done. This will demonstrate deposition of eosinophilic granular material in the media of small arteries and arterioles. The MRI of a patient with CADASIL will show hyperintensities of the white matter, especially in the anterior temporal poles on T2-weighted MRI sequences. As the disease progresses, there is more involvement of the white matter in the periventricular regions and deep white matter. There can also be dilated perivascular spaces and microhemorrhages.[9]

Mutations in *HTRA1* cause cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL). CARASIL causes gait disturbance, spasticity, early strokes, mood changes, cognitive decline, and white matter changes in the brain. Premature alopecia and back pain are also seen in this condition.

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) can also cause migraine-type headaches, early dementia, seizures, and stroke. Most cases of MELAS are caused by mutations in the *MT-TL1* (transfer RNA mitochondrial, leucine 1) gene.

Mutations in the gene *TREX1* cause retinal vasculopathy with cerebral leukodystrophy, which is also associated with small-vessel disease, migraine-like headaches, stroke, and dementia.

Mutations in *COL4A1* (collagen type IV, alpha 1) also cause small-vessel disease. A syndrome of hereditary angiopathy with nephropathy, aneurysms, and muscle cramps is caused by mutations in this gene.

Mutations in the *GLA* gene lead to Fabry disease, which is a metabolic cause of early stroke. Fabry disease is a lysosomal storage disorder that results from deficiency of α-galactosidase A. It is X-linked recessive. In this condition, globotriaosylceramide accumulates in cells. Patients can have white matter abnormalities and dolichoectasia of cerebral vessels in addition to stroke. Patients can also have cardiomyopathy, cardiac conduction defects, autonomic dysfunction, and renal failure. Fabry disease produces a small-fiber neuropathy. Angiokeratoma in a bathing suit distribution and painful acroparesthesias are characteristic. Enzyme replacement therapy is available.

Mutations in the *KRIT1* (or *CCM1*) gene are one cause of familial cerebral cavernous malformations.

**31. C**

Watershed infarctions occur when there is a reduction of blood supply between two vascular territories, which makes this area susceptible to ischemia. If the artery that supplies both of these territories is stenosed proximally, then this area of the brain can be affected by low perfusion (due to hypotension, dehydration, infection, etc.). In the patient presented in this question, the infarct is affecting the watershed region of the left ACA and left MCA. The stroke would be due to high-grade stenosis of the left ICA, which is proximal to both these vessels. Paradoxical embolism, cardioembolism from a cardiac thrombus, and M1 stenosis would not cause a watershed infarct between the ACA and MCA.[9]

**32.C**

This patient meets all the inclusion criteria for both rtPA and tenecteplase and mechanical thrombectomy. The onset of her symptoms was less than 6 hours prior to arrival, she has an ASPECTS of 10, she has a proximal occlusion, and she has a good functional baseline. Currently, administering intravenous rtPA prior to thrombectomy is a Class 1 Level A recommendation from the 2019 update of the 2018 American Heart Association guidelines for early management of acute ischemic stroke.[1] Tenecteplase is an alternative to rtPA.[4]

**33. B**

There are many anatomical variants of the aortic arch; however, in the prototypic aortic arch, the first branch is the brachiocephalic artery, which then branches into the right subclavian artery and right common carotid artery. The next vessel along the aorta is the left common carotid artery followed by the left subclavian artery. The vertebral arteries branch off of their respective subclavian arteries.

The common carotid artery bifurcates between the fourth and fifth cervical vertebrae.

The left ICA is a branch of the left common carotid artery, which branches directly off the aorta.

The left vertebral artery branches off the left subclavian artery, which directly comes off the aorta.[9]

**34. B**

This patient is experiencing Benedikt syndrome. The lesion occurs to the ventral midbrain/midbrain tegmentum, which affects CN 3, the red nucleus, the substantia nigra, the cerebral peduncle, and the corticospinal tract. Patients with this syndrome can have tremor or choreoathetosis due to the involvement of the red nucleus and hemiparesis due to the involvement of the cerebral peduncle. Symptoms of cranial nerve damage are usually ipsilateral to the lesion.

Wallenberg syndrome is caused by lesions to the lateral medulla.

Injury to the superior cerebellar peduncle alone would not cause injury to CN 3.

Medial midbrain lesions result in Weber syndrome, which is discussed in Question 35.[9]

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**35. A**

This is Weber syndrome. The lesion that causes Weber syndrome affects the medial part of the midbrain, which contains the fibers of CN 3, the corticobulbar tract, the corticospinal tract, and the substantia nigra. Due to the involvement of these structures, symptoms will include an oculomotor palsy, contralateral facial weakness, and contralateral hemiparesis.[9]

**36. D**

This patient is experiencing one-and-a-half syndrome. In this condition, the only horizontal eye movement that can occur is abduction of the contralateral eye, which usually demonstrates nystagmus when abducted. One-and-a-half syndrome occurs with injury to the pons affecting the PPRF or the abducens nucleus plus injury to the adjacent medial longitudinal fasciculus (MLF). Injury to the PPRF or the abducens nucleus causes an ipsilateral palsy of horizontal conjugate gaze. Injury to the MLF causes internuclear ophthalmoplegia. The paramedian perforators supply this area of the brain; thus, a stroke affecting these vessels can cause one-and-a-half syndrome.[9]

**37. B**

This patient has suffered a right vertebral artery dissection that is producing symptoms of Wallenberg syndrome/lateral medullary syndrome. The most common site of vertebral dissection is at the C1–C2 level, where the vertebral artery leaves the transverse foramina to enter the cranium. The artery is very mobile at this point, which can cause a dissection. MRA of the circle of Willis, carotid ultrasound, and a transthoracic echocardiogram would not show the injury to the vertebral artery. However, a catheter angiogram of the cervicovertebral arteries will be able to visualize the dissection clearly.[26]

**38. C**

Cerebral aneurysms can occur on any intracranial artery; however, the most common locations of saccular berry aneurysms are in the arteries that make up the circle of Willis and the branch points. This includes the distal ICA, the M1 segments of the MCAs, the A1 segments of the ACAs, the anterior communicating artery, the P1 segments of the PCAs, and the posterior communicating arteries. Other common locations for aneurysms are where the MCA branches into the M2 segments, the basilar apex, and the bifurcation site of the vertebral arteries into the posterior inferior cerebellar arteries.[9]

**39. D**

This patient is experiencing reversible cerebral vasoconstriction syndrome (RCVS) in the setting of drug use and antidepressant treatment. The clinical features of RCVS include a thunderclap headache that reaches peak intensity within 1 minute or severe recurrent headaches. In addition, there is cerebral vasoconstriction in at least two different arteries and resolution of the vasoconstriction by 3 months. RCVS is associated with pregnancy and puerperium; exposure to drugs such as cocaine, cannabis, amphetamines, and Ecstasy; and medications such as SSRIs, triptans, pseudoephedrine, tacrolimus, and cyclophosphamide. Complications of RCVS include ischemic stroke, intracerebral hemorrhage, seizures, and focal neurologic findings. Treatment of this condition includes removing any vasoactive agents and avoiding triggers and precipitants. Medications such as calcium channel blockers can also help alleviate the acute headache caused by vasoconstriction.[27]

**40. C**

Medial medullary syndrome is usually caused by an occlusion of the ipsilateral vertebral artery or a branch of the vertebral artery. This stroke will affect the medial lemniscus, hypoglossal nucleus, and corticospinal tract. Symptoms that are seen in patients with this syndrome include ipsilateral tongue weakness with deviation of the tongue toward the weak side when the tongue is protruded, contralateral loss of position and vibration due to the involvement of the medial lemniscus, and contralateral hemiparesis of the arm and leg. The face is typically spared.

**41. A**

Rivaroxaban and apixaban are direct factor Xa inhibitors. Rivaroxaban has a half-life of 5–9 hours and is 95% protein bound. Rivaroxaban was compared to warfarin in the ROCKET AF trial, where it was found to be noninferior in preventing strokes and systemic embolism in patients with nonvalvular atrial fibrillation.[20]

Clopidogrel is a P2Y12 receptor antagonist that inhibits platelet aggregation.

Dabigatran is a director thrombin inhibitor. Idarucizumab has been approved as a reversal agent for dabigatran.

Warfarin antagonizes the vitamin K–dependent clotting pathway. Activated vitamin K is needed to activate factors II (prothrombin), VII, IX, X, protein C, and protein S.[19,20] (See Table 3.1.)

*Table 3.1* MECHANISM OF ACTION OF ANTICOAGULANTS AND ANTIPLATELET AGENTS

| MEDICATION | MECHANISM OF ACTION |
|---|---|
| **Apixaban** | **Factor Xa inhibitor** |
| **Clopidogrel** | **Prevents binding of ADP to the P2Y12 receptor on platelets. This prevents ADP-mediated activation of the GPIIb/IIIa complex.** |
| **Dabigatran** | **Thrombin inhibitor** |
| **Rivaroxaban** | **Factor Xa inhibitor** |
| **Warfarin** | **Antagonizes the vitamin K–dependent clotting pathway** |

**42. D**

The ASPECTS is a quantitative score that measures the extent of early ischemic changes seen on a CT scan. Every CT starts with a baseline score of 10. One point is subtracted for every area that has changes associated with early ischemia. The areas that are assessed in this scale include the caudate head, internal capsule, lentiform nucleus, insular ribbon, anterior MCA cortex (M1), MCA cortex lateral to the insular ribbon (M2), posterior MCA cortex (M3), anterior MCA cortex that is rostral to the M1 (M4), lateral cortex rostral to the M2 (M5), and the posterior cortex rostral to the M3 (M6). The thalamus is not involved in calculating the ASPECTS.[28]

**43. B**

This patient is experiencing a central retinal artery occlusion (CRAO). CRAO presents with painless monocular vision loss. An acute occlusion of the central retinal artery or its parent vessel, the ophthalmic artery, can result in hypoperfusion to the retina, leading to vision loss in the affected eye. Three types of emboli can cause a CRAO: cholesterol, platelet fibrin, and calcium. The first two are thought to come from atheromas that can form in large arteries such as the carotid arteries, and the calcium emboli are thought to originate from the heart, specifically the valves. The classic CRAO finding on fundoscopy is a cherry-red spot on top of a pale retina, which is due to collateral blood supply from the choroidal circulation. An MRI of the brain will be negative for intracerebral ischemia because the occlusion is of the ophthalmic artery and its branches, not the intracerebral branches of the ICA. In this patient's case, the etiology of her CRAO is platelet fibrin emboli from the stenosed right ICA to the ophthalmic artery.[29]

A branched retinal artery occlusion occurs when a branch of the central retinal artery is occluded by an embolism. The entire vision in the affected eye is not lost, but a segment of visual field in that eye will have significant deficit.[29]

**44. B**

The ABCD2 score was designed to estimate the risk of stroke after a TIA. Points are assigned to each part of the score, including age, blood pressure at the time of assessment, clinical features of the TIA, duration of the symptoms, and history of diabetes. (See Box 3.5.) The gender of the patient has no bearing on the ABCD2 TIA score. Higher ABCD2 scores indicate a higher risk of stroke at 2, 7, and 90 days after the TIA event.[30]

### *Box 3.5* CALCULATION OF THE ABCD2 SCORE

- Age >60 years gets a score of 1.
- Blood pressure greater than 140/90 mm Hg gets a score of 1.
- Unilateral weakness gets a score of 2.
- Speech disturbance (without weakness) gets a score of 1.
- Symptom duration: <10 minutes gets a score of 0, 10–59 minutes gets a score of 1, and >60 minutes gets a score of 2.
- History of diabetes gets a score of 1.

**45. A**

Dissection of the carotid artery can cause Horner syndrome. Due to the anatomy of the oculosympathetic pathway, anhidrosis is not typical of carotid artery dissection. Symptoms that are seen with ICA dissection include ptosis, miosis, headache, neck pain, and focal neurologic deficits associated with the stroke.[9]

Horner syndrome consists of ptosis, miosis, and anhidrosis. It is caused by abnormalities in the oculosympathetic pathway. This pathway involves three neurons. The sympathetic fibers travel from the hypothalamus, where the first neuron is located, through the brainstem and spinal cord and synapses between C8 and T2, also known as the ciliospinal center of Budge. The preganglionic, second-order fibers, exit the spinal cord and travel through the cervical sympathetic chain and then over the apex of the lung. They then synapse in the superior cervical ganglion, which is near C4–C5, where the common carotid artery bifurcates. The postganglionic, third-order fibers travel with the ICA into the cavernous sinus and then into the eye. The sympathetic fibers that are responsible for sweating travel with the external carotid artery; thus, anhidrosis is not seen with dissection of the ICA.[9] (See Figure 3.2.)

**46. A**

A stroke in the AICA distribution causes the lateral pontine syndrome.

Medial medullary syndrome may be caused by an anterior spinal artery stroke or a stroke involving branches of the vertebral artery. Medial medullary syndrome affects the pyramid, medial lemniscus, and hypoglossal nerve. Patients have contralateral weakness, usually sparing the face; ipsilateral tongue weakness; and contralateral loss of position and vibration sense.

A stroke in the PICA territory can cause a cerebellar stroke or a lateral medullary syndrome.

A stroke in the distribution of the paramedian branches of the basilar artery causes medial inferior pontine syndrome. The medial lemniscus, corticospinal tract, and abducens nerve roots are affected.

**47. D**

A stroke in the superior division of the right MCA causes left face and arm weakness and left hemineglect in a left hemisphere dominant person. There may also be sensory loss in the face and arm. This is not a lacunar stroke syndrome. The other clinical scenarios are consistent with lacunar stroke. (See Question 13.)

**48. C**

This patient has homocystinuria, which is associated with thromboembolism, eye abnormalities (myopia or lens dislocation), and Marfanoid habitus.

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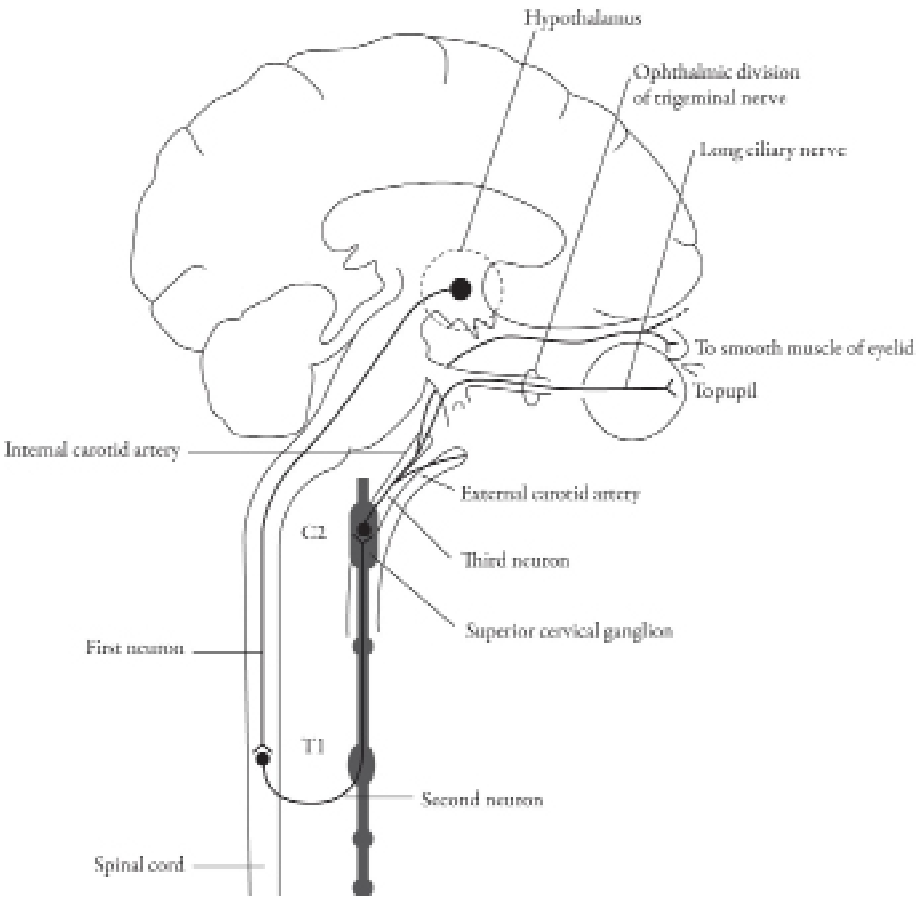

**Figure 3.2** Sympathetic pupil pathway. C2, second cervical vertebra; T1, first thoracic vertebra. SOURCE: From Sundaram V, Barsam A, Alwitry A, Khaw P. *Training in Ophthalmology*, Fig. 9.2. New York: Oxford University Press; 2009.

The most common cause of homocystinuria is cystathionine β-synthase (CBS) deficiency. Some patients with this condition respond to pyridoxine. Patients with homocystinuria due to CBS deficiency are at risk for other conditions, such as dystonia, livedo reticularis, and pancreatitis.

Patients with homocystinuria who do not respond to pyridoxine can be treated with vitamin $B_{12}$ and folate, which help convert homocysteine to methionine. The medication betaine has a similar effect.

Some forms of homocystinuria are associated with megaloblastic anemia. Homocystinuria can be found in some patients with methylmalonic acidemia.

**49. B**

The Stroke Prevention Trial in Sickle Cell Anemia determined that maintaining a hemoglobin S concentration less than 30% of the total hemoglobin concentration reduced the risk for first stroke in patients with sickle cell disease who had rapid flow in the internal or middle cerebral artery on transcranial Doppler ultrasonography. Iron overload is a possible complication.[31]

**50. A**

This patient has hereditary hemorrhagic telangiectasia (HHT), which is also called Osler–Weber–Rendu disease. Most patients present with epistaxis. Patients with HHT can have arteriovenous malformations in multiple organs, such as the brain, lungs, or liver. Patients can have stroke due to a cerebral arteriovenous malformation, cerebral aneurysm, or paradoxical emboli. Some have gastrointestinal bleeding. Telangiectasias can be seen on the skin. Mutations in *ENG*, the gene that encodes endoglin, cause HHT type 1.

Defects in hamartin and tuberin occur in patients with tuberous sclerosis complex (TSC1 and TSC2, respectively).

Defects in merlin occur in patients with neurofibromatosis type 2 (NF2-related schwannomatosis).

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# 4.

# CONGENITAL DISORDERS INCLUDING NEUROCUTANEOUS DISORDERS

## QUESTIONS

1. **Which of the following gives rise to the central nervous system?**
   A. Ectoderm
   B. Endoderm
   C. Mesoderm

2. **Failure of the anterior neural tube to close results in which of the following?**
   A. Alobar holoprosencephaly
   B. Anencephaly
   C. Aprosencephaly
   D. Atelencephaly

3. **Which of the following is least likely to be associated with an encephalocele?**
   A. Meckel–Gruber syndrome
   B. Walker–Warburg syndrome
   C. Chiari II malformation
   D. Chiari III malformation

4. **Which of the following is most likely to be seen in a patient with cyclopia, anosmia, and a central tooth?**
   A. Chiari II malformation
   B. Holoprosencephaly
   C. Porencephaly
   D. Schizencephaly

5. **Which of the following can cause polymicrogyria?**
   A. In utero cytomegalovirus (CMV) infection
   B. Peroxisomal disorders
   C. Mutations in tubulin genes
   D. All of the above

6. **A female with a history of agenesis of the corpus callosum develops infantile spasms. Besides neurology, which of the following specialties should be consulted?**
   A. Nephrology
   B. Cardiology
   C. Ophthalmology
   D. Otolaryngology

7. **Which of the following is least likely to cause microcephaly?**
   A. Achondroplasia
   B. Miller–Dieker syndrome
   C. Velocardiofacial syndrome
   D. Wolf–Hirschhorn syndrome

8. **Which of the following is least likely to cause macrocephaly?**
   A. Sotos syndrome
   B. Rett syndrome
   C. Aqueductal stenosis
   D. Alexander disease

9. **Mutation of which gene is least likely to cause lissencephaly?**
   A. *ARX*
   B. *DCX*
   C. *PCDH19*
   D. *TUBA1A*

10. **A 6-month-old child presents with infantile spasms. He has facial asymmetry and a whirled hypopigmented lesion on his trunk that follows Blaschko lines. Magnetic resonance imaging (MRI) shows hemimegalencephaly. What is the most likely diagnosis?**
    A. Tuberous sclerosis complex (TSC)
    B. Hypomelanosis of Ito
    C. Incontinentia pigmenti
    D. Proteus syndrome

11. **Which of the following should be performed in a patient diagnosed with periventricular nodular heterotopia due to a filamin A defect?**
    A. Echocardiography
    B. Hearing screen
    C. Ophthalmology examination
    D. Renal ultrasound

12. **A full-term female newborn was admitted to the neonatal intensive care unit for vesicular skin lesions. The skin lesions follow Blaschko lines. The pregnancy was uncomplicated. The patient has been well-appearing since birth. The blood and cerebrospinal fluid (CSF) polymerase chain reaction were negative for herpes simplex virus-1 (HSV-1) and HSV-2. Family history revealed a male fetal loss on the maternal side of the family. Which of the following genes is most likely affected in this patient?**
    A. *ARG1*
    B. *VHL*
    C. *IKBKG* (*NEMO*)
    D. *L1CAM*

**13. A child underwent an MRI of the brain, which revealed agenesis of the cerebellar vermis and cystic dilatation of the fourth ventricle. Dandy–Walker syndrome is suspected. Which of the following is also expected to be present in this syndrome?**

A. Midbrain atrophy
B. Pontocerebellar hypoplasia (PCH)
C. Optic nerve hypoplasia
D. An enlarged posterior fossa with an elevated tentorium

**14. A newborn has a lumbar myelomeningocele. Which of the following is most likely to occur with this condition?**

A. Chiari I malformation
B. Chiari II malformation
C. Klippel–Feil syndrome
D. Diastematomyelia

**15. A patient with a history of Chiari I malformation presents with decreased sensitivity to pain in her arms. On examination, she is noted to have decreased pain and temperature sensation in her upper extremities. However, vibration, position, and light touch sensation are intact. What is the most likely diagnosis?**

A. Anterior spinal artery stroke
B. Syrinx
C. Bilateral carpal tunnel syndrome
D. Vitamin $B_{12}$ deficiency

**16. Caudal agenesis is most likely to occur in patients born to mothers with which of the following conditions?**

A. Diabetes
B. Hypothyroidism
C. Hyperthyroidism
D. Rickets

**17. In which condition is a molar tooth seen on brain MRI?**

A. Joubert syndrome
B. COACH syndrome
C. CORS syndrome
D. All of the above

**18. Regarding craniosynostosis, which of the following statements is correct?**

A. The most common cause of plagiocephaly is craniosynostosis.
B. The most common type of craniosynostosis is lamboid synostosis.
C. Mutations in fibroblast growth factor receptors can cause craniosynostosis.
D. Hypothyroidism is a common cause of craniosynostosis.

**19. A 9-year-old girl presents with attention-deficit/hyperactivity disorder. On examination, she has macrocephaly, 10 café-au-lait spots more than 5 mm, and a tibia deformity. Which of the following is least likely to occur in this condition?**

A. Renal artery stenosis
B. Pulmonary lymphangioleiomyomatosis
C. Moyamoya disease
D. Iris hamartomas

**20. A 20-year-old man presents with decreased hearing and unsteadiness. His father has a history of meningioma and cataracts from a young age. Masses are seen in the cerebellopontine angle bilaterally on the patient's brain MRI. What is the diagnosis?**

A. Neurofibromatosis type 1 (NF type 1)
B. Neurofibromatosis type 2 (NF type 2)
C. Von Hippel–Lindau disease
D. Sturge–Weber syndrome
E. Schwannomatosis

**21. An infant with hypopigmented lesions undergoes echocardiography for a heart murmur and is found to have cardiac rhabdomyomas. The electrocardiogram shows Wolff–Parkinson–White syndrome. Which of the following is *least* likely to be seen on the brain MRI?**

A. Cortical tubers
B. Subependymal nodules
C. Subependymal giant cell astrocytomas (SEGAs)
D. Hemangioblastoma

**22. A patient with tuberous sclerosis complex develops infantile spasms. Which of the following is the best treatment?**

A. Adrenocorticotropic hormone (ACTH)
B. The ketogenic diet
C. Topiramate
D. Vigabatrin
E. Zonisamide

**23. A patient with a port-wine stain involving the first division of the trigeminal nerve develops seizures. Head computed tomography shows dystrophic calcifications. Which of the following ophthalmic diseases is the patient most likely to have?**

A. Cataract
B. Coloboma
C. Glaucoma
D. Optic nerve hypoplasia

**24. A 3-year-old girl presents with wide-based gait and increased falls. She has a history of recurrent upper and lower respiratory infections. Her mother says her eyes seem irritated and red all the time. On exam, she is ataxic. Immunoglobulin G (IgG), IgE, and IgA levels are low. Which of the following is least likely to occur in this condition?**

A. Lymphoma
B. Chorea
C. Oculomotor apraxia
D. Decreased α-fetoprotein (AFP) level

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# CONGENITAL DISORDERS INCLUDING NEUROCUTANEOUS DISORDERS

## ANSWERS

**1. A**

The embryo is formed from three germ layers: ectoderm, endoderm, and mesoderm. The ectoderm gives rise to the central nervous system and skin. The endoderm forms the digestive system (intestines) and lungs. The mesoderm becomes the musculoskeletal system, kidneys, heart, and blood.

**2. B**

Failure of the anterior neural tube to close can cause anencephaly. This usually occurs between 18 and 24 days of embryonic development. (The anterior neuropore usually closes on day 25.) The lamina terminalis is where the anterior neuropore closes. It becomes a part of the wall of the third ventricle.

Folate helps prevent neural tube defects. Menstruating women who are taking an anti-seizure medication should be placed on folate. Women with mutations in the *MTHFR* gene, which encodes methylenetetrahydrofolate reductase, may require higher doses of folate to prevent neural tube defects. Mutations in *MTHFR* can cause anencephaly, spina bifida, and homocystinuria.

Regarding aprosencephaly, atelencephaly, and holoprosencephaly, refer to Question 4.

**3. C**

Encephaloceles represent a restricted defect in anterior neural tube closure that allows protrusion of brain and its coverings.

Meckel–Gruber syndrome is characterized by an occipital encephalocele, cleft lip and palate, polycystic kidneys, and polydactyly. It is a ciliopathy (a disease with cilia dysfunction).

Walker–Warburg syndrome is a form of congenital muscular dystrophy associated with eye abnormalities and brain malformations including encephalocele.

Chiari III malformation is associated with an encephalocele, whereas Chiari II malformation is nearly always related with a myelomeningocele, not an encephalocele.

**4. B**

During development, the neural tube undergoes segmentation, which creates the prosencephalon, mesencephalon, and rhombencephalon. The prosencephalon gives rise to the forebrain; the mesencephalon gives rise to the midbrain; and the rhombencephalon gives rise to the hindbrain.

Prosencephalic development involves prosencephalic formation, prosencephalic cleavage, and midline prosencephalic development.

Normally, the prosencephalon is formed from the rostral end of the neural tube and divides into the telencephalon and diencephalon. The telencephalon becomes the cerebral hemispheres, and the diencephalon gives rise to the thalamus and hypothalamus. Aprosencephaly and atelencephaly are disorders of prosencephalic formation. In aprosencephaly, neither the telencephalon nor the diencephalon form. In atelencephaly, the telencephalon does not form, but the diencephalon is present.

Failure of prosencephalic cleavage causes holoprosencephaly.

The most severe form of holoprosencephaly is alobar holoprosencephaly. There is no separation of the hemispheres, no interhemispheric fissure, and no corpus callosum. There is a single midline ventricle, and the basal ganglia and thalami are fused. The patient may have cyclopia, and the olfactory bulbs and tracts are absent. The septum pellucidum is absent in all types of holoprosencephaly.

Semilobar holoprosencephaly is the intermediate form of holoprosencephaly. There is some division of the cerebral hemispheres posteriorly. The anterior corpus callosum is absent.

Lobar holoprosencephaly is less severe. There is almost complete separation of the hemispheres except in the most ventral and rostral portion. The anterior corpus callosum may be underdeveloped.

A cleft lip/palate or a central tooth can be seen in holoprosencephaly. Diabetes insipidus, as well as other endocrinopathies, can occur in patients with holoprosencephaly.

There are multiple environmental and genetic causes of holoprosencephaly. Maternal diabetes is a risk factor. Holoprosencephaly is seen in trisomy 13 and 18 and in Smith–Lemli–Opitz, Pallister–Killian, Rubenstein–Taybi, and Kallmann syndromes. Mutations in *SHH* and *ZIC2* have been found in patients with holoprosencephaly.

Schizencephaly is characterized by a cleft in the cortical surface that is lined in gray matter and extends

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toward the ventricle. It is thought to be caused by vascular injury or infection.

Porencephaly refers to an intraparenchymal cyst that communicates with the ventricle. Mutations in *COL4A1* cause hereditary porencephaly. Mutations in this gene also cause the conditions brain small-vessel disease (with or without ocular anomalies) and hereditary angiopathy with nephropathy, aneurysms, and muscle cramps (HANAC).

**5. D**

There are multiple causes of polymicrogyria. In utero infection (e.g., with CMV), in utero ischemia, and metabolic diseases such as Zellweger syndrome can cause polymicrogyria. There are also multiple genetic mutations that cause polymicrogyria. Mutations in tubulin, which is required for the formation of microtubules, can cause polymicrogyria as well as other brain malformations. Mutations in *GPR56* cause bilateral frontoparietal polymicrogyria. Mutations in the gene *SRPX2* on chromosome Xq22 can cause bilateral perisylvian polymicrogyria, which is a common form of polymicrogyria. It is associated with seizures and oromotor dyspraxia. Intellectual disability may also be present.

**6. C**

This patient may have Aicardi syndrome. Aicardi syndrome is characterized by the classic triad of agenesis of the corpus callosum, infantile spasms, and chorioretinal lacunae. It is an X-linked dominant condition that usually affects females.

Agenesis of the corpus callosum, agenesis of the septum pellucidum, and septo-optic dysplasia are disorders of midline prosencephalic development. There are genetic, metabolic, and environmental causes of agenesis of the corpus callosum. Agenesis of the corpus callosum can occur as part of syndrome or independently. Other midline defects may also be present. For instance, agenesis of the corpus callosum, congenital heart defects, Hirschsprung disease, and genitourinary anomalies are seen in Mowat–Wilson syndrome, which is caused by mutations in *ZEB2*.

**7. A**

Achondroplasia causes megalencephaly and macrocephaly. It results from mutations in *FGFR3* and is autosomal dominant. It causes short stature with shortening of the proximal limbs, lumbar lordosis, hypotonia, and developmental delay. Cervicomedullary compression can result in early death. Hydrocephalus can occur due to stenosis of the jugular foramina.

Miller–Dieker syndrome is caused by mutations in chromosome 17p13.3 that include the *LIS1* gene (*PAFAH1B1*) and the gene *YWHAE*. Patients have microcephaly, lissencephaly, a furrowed brow, and cardiac defects.

Velocardiofacial syndrome is a chromosome 22q11.2 deletion syndrome. The term CATCH-22 has been used for the 22q11.2 deletion syndromes, which also include DiGeorge syndrome and Cayler cardiofacial syndrome. CATCH stands for cardiac abnormality, anomalous face, thymus hypoplasia, cleft palate, and hypocalcemia.

Wolf–Hirschhorn syndrome is caused by chromosome 4p monosomy. Patients with Wolf–Hirschhorn syndrome have "Greek warrior helmet" facies, microcephaly, seizures, hypotonia, and intellectual disability. Skeletal and cardiac anomalies may also be present.

**8. B**

Rett syndrome is an X-linked dominant neurodevelopmental disorder that predominantly affects females. It is associated with acquired microcephaly, epilepsy, and intellectual disability. Abnormal repetitive hand movements are a hallmark of Rett syndrome.

Sotos syndrome is an overgrowth genetic condition and is characterized by macrocephaly, characteristic facial features (prominent forehead, down-slanting palpebral fissures, and long face), and various degrees of learning disabilities.

Alexander disease is a rare neurodegenerative disease. This leukodystrophy is caused by a mutation in the *GFAP* gene, which codes for glial fibrillary acidic protein (GFAP). Rosenthal fibers, which contain GFAP, accumulate in many regions, including the deep white matter, brainstem, and spinal cord. Demyelination usually begins in the frontal regions. Clinically, Alexander disease causes macrocephaly, seizures, and delay or regression of development.

Aqueductal stenosis is a common cause of congenital hydrocephalus, which may lead to macrocephaly. Mutations at Xq28 in *L1CAM*, which encodes for L1 cell adhesion molecule, cause hydrocephalus due to aqueductal stenosis; CRASH syndrome; MASA syndrome; and hydrocephalus with Hirschsprung disease. CRASH stands for corpus callosum hypoplasia, mental retardation, adducted thumbs, spastic paraplegia, and hydrocephalus. MASA stands for mental retardation, aphasia, shuffling gait, and adducted thumbs. MASA syndrome is also known as spastic paraplegia-1.

Other causes of neonatal hydrocephalus include myelomeningocele, communicating hydrocephalus, and Dandy–Walker syndrome. These conditions also cause fetal hydrocephalus. In addition, holoprosencephaly is a major cause of fetal hydrocephalus.

**9. C**

Mutations in *LIS1* (*PAFAH1B1*) on chromosome 17, *DCX* on the X chromosome, and *TUBA1A* can cause classic lissencephaly, which is characterized by a thick, four-layer cortex rather than a six-layer cortex. Specifically, mutations in *DCX*, which encodes doublecortin, cause lissencephaly in males and subcortical band heterotopia in females. *LIS1* (*PAFAH1B1*) and *DCX* regulate the function of microtubules, which are required for cell division.

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Mutations in *TUBA1A* and *TUBG1*, which result in tubulinopathies, cause lissencephaly and microlissencephaly (i.e., lissencephaly plus a head circumference <3 standard deviations below the mean). Dysmorphic basal ganglia are typical of tubulinopathies. Cerebellar anomalies are also common. Agenesis of the corpus callosum can occur.

Mutations in *TUBA1A* can cause lissencephaly with cerebellar hypoplasia. Mutations in *RELN* can also cause this condition.

In classic lissencephaly, which is also known as type 1 lissencephaly, there is undermigration of neurons. Overmigration of neurons causes cobblestone cortical malformation, which is also known as cobblestone lissencephaly or type 2 lissencephaly. This is seen in Fukuyama congenital muscular dystrophy, Walker–Warburg syndrome, and muscle–eye–brain disease. Cobblestone cortical malformation is caused by defects in the O-linked glycosylation of α-dystroglycan.

Mutations in the gene *ARX*, which is a homeobox gene, cause X-linked lissencephaly-2. X-linked lissencephaly-2 is associated with a three-layer cortex. Ambiguous genitalia and agenesis of the corpus callosum can also occur in this condition. X-linked lissencephaly-2 has also been called X-linked lissencephaly with ambiguous genitalia or XLAG. Mutations in *ARX* can also cause X-linked intellectual disability and X-linked early infantile epileptic encephalopathy-1, which has also been known as X-linked infantile spasm syndrome-1.[1,2]

Mutations in *PCDH19*, which encodes protocadherin, cause an early onset X-linked epileptic encephalopathy in females that can be associated with autism and intellectual disability.

## 10. B

This patient has hypomelanosis of Ito (HI), which is a neurocutaneous disorder. Some patients with HI have hemimegalencephaly. Patients with HI are at risk for seizures, including infantile spasms. Intellectual disability is common. Facial or limb asymmetry may be present. Eye, hair, and dental abnormalities can also occur. The pathogenesis of HI is unknown but is likely to be multifactorial. A specific gene has not been identified. Chromosomal mosaicism has been seen in patients with HI.

Other causes of hemimegalencephaly are epidermal nevus syndrome, TSC, and Proteus syndrome.

Incontinentia pigmenti is discussed in Question 12.

## 11. A

Filamin A is involved in initiation of migration. Mutations in the filamin A gene (*FLNA*) can cause X-linked dominant periventricular nodular heterotopia. Some of the patients with this mutation have an aortic aneurysm. Therefore, an echocardiogram should be obtained at the time of diagnosis.

## 12. C

Incontinentia pigmenti (IP), also known as Bloch–Sulzberger syndrome, is a rare X-linked dominant neurocutaneous disorder. In most cases, it results from X-inactivation due to mutation in the gene *IKBKG*, which was formerly known as *NEMO* (NF-κB essential modulator). The deletional mutation is typically lethal for the male fetus, so cases are predominantly female.

IP is characterized by skin lesions with vesicles and pustules that appear in the first 3 weeks of life and are distributed along the Blaschko lines. Possible extracutaneous findings include alopecia and ocular, skull, and dental abnormalities. Neurological findings include seizures, developmental delay, cognitive impairment, cerebral dysgenesis, stroke, microcephaly, corpus callosum abnormalities, and acute disseminated encephalomyelitis.[3,4]

Clinically, IP can be confused with neonatal HSV-1 infection given similar cutaneous manifestations.

## 13. D

Dandy–Walker syndrome is a triad of agenesis of the cerebellar vermis, cystic dilatation of the fourth ventricle, and an enlarged posterior fossa with an elevated tentorium. Other anomalies, such as agenesis of the corpus callosum, heterotopia, syringomyelia, and cardiac and urogenital anomalies, may also be present. Hydrocephalus occurs in most patients. Cognitive abilities are variable.

Mega cisterna magna is often confused with Dandy–Walker syndrome. Both are associated with an enlarged posterior fossa; however, in patients with a mega cisterna magna, the fourth ventricle and cerebellar vermis are normal.

There are multiple forms of pontocerebellar hypoplasia (PCH). In PCH, the cerebellar hemispheres may be more affected than the vermis.

## 14. B

Myelomeningocele is caused by failure of the posterior neural tube to close. In patients with myelomeningocele, the meninges and neural tissue protrude through a vertebral defect and may be visible on physical examination. Folic acid helps prevent this condition.

A Chiari II malformation is nearly always associated with a lumbar myelomeningocele. In patients with a Chiari II malformation, the brainstem, cerebellum, and fourth ventricle are displaced into the upper cervical canal through the foramen magnum, and the tectum can appear beaked. Although the exact cause of Chiari II malformation remains unclear, it is widely believed that the downward traction due to the presence of myelomeningocele contributes to the displacement of the brainstem and cerebellum. After surgical closure of a myelomeningocele, hydrocephalus often occurs, requiring shunting.

A Chiari I malformation is characterized by extension of the cerebellar tonsils at least 5 mm (in adults)

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through the foramen magnum. It can be found incidentally. Patients with Chiari I malformation are often asymptomatic. Occipital headache can occur. Severe cases can cause cervical cord compression and lower cranial nerve deficits. Surgical decompression may be necessary for patients with significant symptoms.

Diastematomyelia refers to division of the spinal cord into two halves.

Klippel–Feil syndrome is characterized by abnormal fusion of cervical vertebrae. This can result in a short neck, low hairline, and decreased neck movement.

**15. B**

Given the history of Chiari I malformation and the distribution of neurological symptoms, a syrinx is the most likely diagnosis. Alteration of CSF flow dynamics in Chiari I malformation may form a fluid-filled pocket or cyst around the center of the spinal cord, commonly referred to as a syrinx.

The patient has evidence of a spinal cord lesion, which manifests with sensory loss in a shawl-like pattern in the upper extremities. Symptoms result from involvement of crossing spinothalamic fibers due to the presence of syrinx. The posterior columns are spared; therefore, vibration, pinprick, and light touch sensation are intact.

Anterior spinal artery stroke typically causes abrupt loss of motor function below the affected level and decreased pain and temperature sensation; however, the posterior columns are spared.

Vitamin $B_{12}$ deficiency causes a posterolateral column syndrome in which the dorsal columns and corticospinal tracts are affected. Pain and temperature are intact in this condition because the spinothalamic tracts are preserved.

**16. A**

The term *caudal agenesis* refers to abnormal development of the sacrum and coccyx. Abnormalities of the legs, gastrointestinal tract, or genitourinary tract may be present. Maternal diabetes is a risk factor. Caudal agenesis is also referred to as caudal regression syndrome. However, the caudal vertebrae in this condition do not regress but in fact never develop.

**17. D**

A molar tooth is a midbrain abnormality seen in Joubert, COACH, CORS, and oral–facial–digital syndrome type VI syndromes. Lack of decussation of superior cerebellar tract fibers produces an abnormal configuration of the superior cerebellar peduncles, which gives the appearance of a molar tooth.

Patients with Joubert syndrome have developmental delay, hypotonia, ataxia, and hypoplasia of the vermis. Irregular breathing and abnormal eye movements can also be seen. There are multiple forms of Joubert syndrome, some of which are associated with other systemic abnormalities. For example, hepatic fibrosis can occur in Joubert syndrome due to mutations in *TMEM67*. Joubert syndrome is considered a ciliopathy, as are Bardet–Biedl and Meckel syndromes.

COACH stands for cerebellar vermis hypo/aplasia, oligophrenia (intellectual disability), ataxia, ocular coloboma, and hepatic fibrosis.

CORS stands for cerebellooculorenal syndrome.

**18. C**

The most common type of plagiocephaly is positional plagiocephaly.

Premature closure of one or more sutures causes craniosynostosis. The most common craniosynostosis is sagittal synostosis due to premature closure of the sagittal suture, which causes the skull to elongate in the anterior–posterior direction (scaphocephaly).

There are multiple causes of craniosynostosis. Systemic diseases such as hyperthyroidism and rickets can cause craniosynostosis. Lack of brain growth can result in craniosynostosis. In addition, mutations in fibroblast growth factor receptors cause multiple conditions with craniosynostosis, such as Apert and Crouzon syndromes.

**19. B**

This patient has NF type 1. She has a bony deformity and the requisite size and number of café-au-lait patches, which are two of the criteria for diagnosis. (Because the patient is prepubertal, she must have at least six café-au-lait patches measuring ≥5 mm to meet the criterion.) Other diagnostic criteria are optic glioma, iris hamartomas (Lisch nodules), axillary and inguinal freckling, neurofibromas and plexiform neurofibromas, and a positive family history.

In 2022, the NF type 1 diagnostic criteria were revised. The revised criteria include genetic testing and choroidal anomalies.[5,6]

Children with NF type 1 who are younger than age 6 years are at the highest risk for developing optic gliomas. Endocrinopathies can occur with hypothalamic extension.[3]

Patients with NF type 1 tend to have macrocephaly and learning problems. They are also at risk for brain tumors, peripheral nerve sheath tumors, and vasculopathy including moyamoya disease. Renal artery stenosis can occur. Blood pressure should be monitored.

Plexiform neurofibromas in NF type 1 patients can undergo malignant transformation. Selumetinib is a kinase inhibitor that is approved by the U.S. Food and Drug Administration (FDA) to treat plexiform neurofibromas that are not completely resectable.

NF type 1 is caused by mutations in the gene *NF1*. *NF1* is found on chromosome 17q and encodes for neurofibromin, which is a tumor suppressor that regulates Ras. NF type 1 is considered a RASopathy.

The RASopathies are syndromes due to mutations in genes that affect the Ras/mitogen-activated protein kinase (MAPK) pathway. Other RASopathies are

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Noonan syndrome, Noonan syndrome with multiple lentigines, capillary malformation–arteriovenous malformation syndrome, cardiofaciocutaneous syndrome, and Legius syndrome.[7] Some patients with Legius syndrome meet criteria for NF type 1.[3] Legius syndrome is associated with multiple café-au-lait patches and is due to mutations in the gene *SPRED1*.[5]

Pulmonary lymphangioleiomyomatosis can occur in TSC.

## 20. B

This patient has NF type 2, which is caused by mutations in *NF2* on chromosome 22. *NF2* encodes merlin. (Merlin is also known as schwannomin.) Bilateral vestibular schwannomas are pathognomonic of NF type 2. (These have also been referred to as acoustic neuromas, but they are in fact schwannomas of the vestibular nerve.)

NF type 2 is also known as MISME syndrome because patients can develop *m*ultiple *i*nherited *s*chwannomas, *m*eningiomas, and *e*pendymomas. Some patients with NF type 2 develop posterior subcapsular cataracts.

Of note, patients with NF type 2 have fewer skin manifestations compared to patients with NF type 1. Therefore, patients with NF type 2 are more likely to present with brain tumors and be diagnosed in middle age, whereas patients with NF type 1 may be recognized in childhood due to skin manifestations.

Schwannomatosis, which is associated with multiple schwannomas, has a phenotype that overlaps with NF type 2. However, patients with schwannomatosis do not have vestibular schwannomas.[3] In addition, schwannomatosis is genetically distinct from NF type 2. Schwannomatosis may be due to mutations in *SMARCB1* or *LZTR1*, be 22q-related, or be associated with other genetic findings.[8]

In 2022, there was an international consensus recommendation to rename neurofibromatosis type 2 as NF2-related schwannomatosis to reduce confusion between NF type 1 and NF type 2.[8]

## 21. D

This patient has TSC. Brain neuroimaging is recommended. Cortical tubers and subependymal nodules are expected. Patients with TSC can also have subependymal giant cell astrocytomas (SEGAs). Enlarging SEGAs that could obstruct the foramen of Monro may require treatment with a mammalian target of rapamycin (mTOR) inhibitor or surgery.

Patients diagnosed with TSC should undergo MRI of the abdomen to evaluate for renal angiomyolipomas and renal cysts. Renal cell carcinoma can occur in adults with TSC but is rare. Pulmonary lymphangioleiomyomatosis is also a concern in adults with TSC, particularly in women.

Mutations in the gene *TSC1* or *TSC2* cause TSC, which is autosomal dominant. *TSC1* (on 9q) encodes hamartin, and *TSC2* (on 16p) encodes tuberin. Mutations in these genes cause upregulation of the mTOR pathway.

Hemangioblastoma can be seen in patients with von Hippel–Lindau disease.

## 22. D

Vigabatrin is preferred for the treatment of infantile spasms in patients with TSC. However, vigabatrin can cause peripheral visual field defects, so the FDA has recommended frequent ophthalmology evaluations. Vigabatrin can also cause reversible myelinic edema, which is visible in the globi palladi, hypothalamus, and within the central tegmental tracts of the pons on T2-weighted and diffusion-weighted brain MRI.

Patients with TSC should also be followed by ophthalmology because of the risk of retinal hamartomas and retinal depigmentation.

## 23. C

This patient has Sturge–Weber syndrome, which can be caused by a somatic mosaic mutation in the guanine nucleotide-binding protein q gene (*GNAQ*). Typically, patients with Sturge–Weber syndrome have a port-wine-colored vascular nevus in the distribution of the ophthalmic branch of the trigeminal nerve. Patients with this syndrome are at risk for glaucoma (not cataracts). Most have seizures, and many develop a hemiparesis. Developmental delay is common. Sturge–Weber syndrome is associated with leptomeningeal venous angiomas, most often in the occipital or occipitoparietal region. These are associated with subcortical dystrophic calcification, referred to as a "tram-track" pattern on imaging.

## 24. D

This patient has ataxia–telangiectasia, which is caused by mutations in *ATM*. Ataxia–telangiectasia is autosomal recessive. Cerebellar symptoms, such as ataxia, dysarthria, or oculomotor apraxia (difficulty moving the eyes in a desired direction), are present in early childhood. Dystonia, chorea, and myoclonus may also be present. Telangiectasias appear between ages 3 and 6 years. Patients with ataxia–telangiectasia often have a history of recurrent sinopulmonary infections. Neuropathy, premature aging, and diabetes may also be seen. Ataxia–telangiectasia is a disorder of DNA repair. Patients with ataxia–telangiectasia are sensitive to ionizing radiation and are at risk for cancer. Of those who develop cancer, most will develop lymphoma or leukemia. Laboratory studies show an elevated AFP and decreased IgA, IgG, and IgE.

Other DNA repair disorders include ataxia–telangiectasia–like disorder, Cockayne syndrome, xeroderma pigmentosa, spinocerebellar ataxia with axonal neuropathy, Nijmegen breakage syndrome, and trichothiodystrophy.

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# 5.

# CRITICAL CARE AND TRAUMA

## QUESTIONS

1. **A 55-year-old man presents to the emergency department due to altered mental status, nausea, and vomiting. His head computed tomography (CT) demonstrates loss of gyri and sulci and an area of hypodensity with an underlying mass. What is the most likely cause of this finding?**
   - A. Failure of the adenosine triphosphate (ATP)-dependent sodium–potassium membrane ($Na^+/K^+$-ATPase) pump
   - B. Disruption of the blood brain barrier
   - C. Cytotoxic edema
   - D. Interstitial edema

2. **Which of the following is true?**
   - A. Cytotoxic edema is due to the failure of the $Na^+/K^+$-ATPase pump.
   - B. Vasogenic edema is commonly seen in the setting of intracellular fluid accumulation, which leads to cell swelling.
   - C. Cytotoxic edema leads to the destruction of the blood–brain barrier.
   - D. Hypernatremia can result in cerebral edema.

3. **An 80-year-old man suffers a cardiac arrest associated with ventricular fibrillation at home. Emergency medical services performs intubation and 15 minutes of cardiopulmonary resuscitation in the field. Which of the following is true?**
   - A. There is potential benefit of therapeutic hypothermia with a goal temperature of 32–34°C for 24 hours.
   - B. The target temperature of hypothermic therapy is 30–32°C for 48 hours.
   - C. Neurologic outcome in the patient will not improve with therapeutic hypothermia.
   - D. There are no associated complications of therapeutic hypothermia.

4. **Which of the following is most likely to cause cerebral edema?**
   - A. Rapid ascent into high altitude
   - B. Acetazolamide
   - C. Coronary artery disease
   - D. Nonalcoholic fatty liver disease

5. **An 18-year-old man was riding an all-terrain vehicle without a helmet. He hit a ditch and was thrown off the vehicle. He presents with clear fluid from his nose and bruising around his eyes. What is the most likely cause of his exam findings?**
   - A. Skull base injury
   - B. Subdural hematoma
   - C. Epidural hematoma
   - D. Cervical spine fracture

6. **The patient from Question 5 starts to get more confused and lethargic. He starts vomiting and then has a seizure. Increased intracranial pressure (ICP) is confirmed. Which of the following is true?**
   - A. Prolonged hyperventilation should be used with a target partial pressure of $CO_2$ of 15–20 mm Hg.
   - B. Continuous mannitol should be administered with a target serum osmolarity of >330 mOsm/L.
   - C. Hypertonic saline can worsen increased ICP due to creating an osmolar gradient.
   - D. Hyperventilation is not a long-term treatment option for increased ICP.

7. **Which of the following is true regarding hemicraniectomy for a malignant middle cerebral artery (MCA) stroke?**
   - A. It can increase the morbidity and mortality in eligible patients who undergo this procedure.
   - B. It should not be done in any patient older than age 60 years.
   - C. It can be performed with little complications up to 1 week after symptom onset.
   - D. The goal of this procedure is to cause herniation of the brain out of the skull.

8. **Which of the following does *not* contribute to the ICP waveform?**
   - A. Intracranial compliance
   - B. Arterial pulsation
   - C. Cerebrospinal fluid (CSF) pressure
   - D. Aortic valve closure

9. **While in the intensive care unit (ICU), a 90-year-old patient is found to be confused, hallucinating, and pulling at her intravenous (IV) lines. Which of the following describes her condition?**
   - A. Hypoactive delirium
   - B. Acute psychosis
   - C. Hyperactive delirium
   - D. Agitation

10. **A 90-year-old man presents from a nursing home after being found obtunded. A CT of the patient's head shows a large right basal ganglia hemorrhage with intraventricular extension and right-to-left midline shift. The patient's code status is do not resuscitate and do not intubate. What is the next step in management?**

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A. ICP monitor
B. Intraventricular catheter
C. An epidural transducer
D. Palliative care consult and comfort measures

**11. A patient comes into the hospital with altered mental status. His exam deteriorates. He becomes unresponsive and tachycardic, and his pupils are 2 mm in the right eye and 5 mm in the left eye. He does not open his eyes, there is no verbal output, and he is posturing in response to pain. What is the next recommended step in management?**

A. Stat CT
B. Magnetic resonance imaging (MRI) of the brain
C. Endotracheal intubation
D. Start a central line

**12. A 46-year-old patient with a history of end-stage renal disease, hypertension, and hyperlipidemia presents to the hospital due to a witnessed generalized tonic–clonic seizure. Her presenting blood pressure is 200/104 mm Hg. The MRI shows evidence of reversible posterior leukoencephalopathy syndrome (RPLS). What is true about her condition?**

A. Hyperlipidemia is a typical etiology.
B. Eclampsia is not associated with this condition.
C. Edema caused by this condition is only seen on the posterior parts of the brain, specifically the occipital and parietal lobes.
D. The etiology sometimes can be linked to immunosuppressive therapy.

**13. Which condition is most likely to respond to corticosteroids?**

A. Brain tumors
B. Reversible posterior leukoencephalopathy syndrome
C. Acute obstructive hydrocephalus
D. Ischemic stroke

**14. Which of the following statements is true regarding management of increased ICP?**

A. Barbiturates should be the first-line agent in trying to reduce increased ICP.
B. Propofol has a long half-life, which is ideal for lowering ICP.
C. Barbiturates decrease ICP by reducing the metabolic activity of the brain, which results in reduction of the blood volume to the brain.
D. Burst suppression is a detrimental sign for a patient on pentobarbital, and if seen on electroencephalogram (EEG) the medication should be stopped immediately.

**15. What is the etiology of a subdural hematoma?**

A. Rupture of the middle meningeal artery
B. Tearing of the bridging veins of the cerebral surface
C. Lipohyalinosis of the vessels
D. Amyloid deposits in the brain

**16. A 20-year-old woman was seen to have a seizure after taking an unspecified drug at a party. She is diagnosed as having status epilepticus on arrival to the emergency department and is intubated for airway protection. What is the most effective sequence of medications for treatment of her status epilepticus?**

A. Propofol, fosphenytoin, lorazepam, then pentobarbital if needed
B. Levetiracetam, lorazepam, phenytoin, then pentobarbital if needed
C. Lorazepam, fosphenytoin, propofol, then pentobarbital if needed
D. Lorazepam, midazolam, pentobarbital, then fosphenytoin if needed

**17. A 50-year-old woman with polycystic kidney disease presents with a nontraumatic subarachnoid hemorrhage (SAH). She undergoes an endovascular coiling of a right anterior cerebral artery (ACA) aneurysm. Three days after her procedure, she becomes confused and has weakness of her left arm and leg. What is the most likely cause of her symptoms?**

A. Rebleeding
B. Hydrocephalus
C. Seizure
D. Vasospasm

**18. A 38-year-old man with no medical history presents with acute onset of severe headache, nausea, neck stiffness, and declining mental status. By the time his CT is complete, the patient is stuporous and is nearly flaccid in the right arm and leg. CT of the head shows SAH. Based on the patient's presentation, what is his Hunt and Hess classification score?**

A. Hunt and Hess 5
B. Hunt and Hess 4
C. Hunt and Hess 3
D. Hunt and Hess 2

**19. A 40-year-old patient presents with a 5-day history of ascending weakness. He also reports severe diarrhea and back pain. His exam is significant for distal weakness in both lower limbs and absent deep tendon reflexes. CSF studies show 0 red blood cells per microliter, 2 white blood cells per microliter, and protein of 200 mg/dL. Presently, he denies any respiratory distress, fatigue, or weakness in his oropharynx. What is the next step in treatment?**

A. High-dose corticosteroids
B. Intubate the patient due to expectant respiratory decompensation.
C. Start intravenous immunoglobulin (IVIG) therapy.
D. Refer the patient for acute rehabilitation.

**20. A 50-year-old woman with a history of myasthenia gravis, chronic lumbar pain, and severe depression presents via emergency medical services due to altered mental status, myoclonus, tachycardia, hyperreflexia, muscle rigidity, and hyperactive bowel sounds. Her medications include pyridostigmine four times a day, tramadol for pain, sertraline for depression, amitriptyline for tension headaches, and trazodone to**

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**help her sleep. What is the most likely cause of her presentation?**

A. Cholinergic crisis
B. Myasthenic crisis
C. Adrenergic crisis
D. Serotonin syndrome

21. **A 60-year-old man with a history of chronic alcoholism presents to the emergency department due to a withdrawal seizure. The patient is significantly hyponatremic. He is started on thiamine and 3% normal saline. On the fifth day of the patient's hospitalization, he develops dysphagia, lethargy, and profound generalized weakness. There is an acute abnormality seen on his brain imaging. Where is the acute abnormality most likely to be?**

A. Central pons
B. Mamillary bodies
C. Bilateral thalami
D. Ventral pons

22. **A 20-year-old man presents to the emergency department after a motor vehicle accident. He has a femur fracture. On exam, he has multiple small hemorrhages on his skin, especially in the axillary region. He becomes obtunded during the exam. What is the most likely cause of his symptoms?**

A. Disseminated intravascular coagulation
B. Fat embolism
C. Epidural hematoma
D. Thrombotic thrombocytopenic purpura

23. **A 70-year-old woman with a history of schizoaffective disorder and hypertension presents to the emergency department due to altered mental status. The patient presents with her aide, who states she has been acting strange following medication adjustments. The patient has a very high fever and is rigid and lethargic. She is unable to answer any questions. What is the most likely diagnosis?**

A. Urinary tract infection
B. Meningococcal meningitis
C. Serotonin syndrome
D. Neuroleptic malignant syndrome (NMS)

24. **Which medication should be considered to prevent complications of SAH due to aneurysm rupture?**

A. Clonidine
B. Hydralazine
C. Nimodipine
D. Amlodipine

25. **A patient with a ruptured MCA berry aneurysm is seen to have extensive subarachnoid bleeding with extension into the ventricles. What is the correct grade for the description of bleeding?**

A. Hunt and Hess grade III
B. Fisher grade III
C. Hunt and Hess grade IV
D. Fisher grade IV

26. **A 75-year-old man with valvular atrial fibrillation is on warfarin for treatment. He presents to the emergency department due to altered mental status. CT of the head shows a large intraparenchymal hemorrhage with midline shift. His international normalized ratio (INR) is 5. What should be given in addition to vitamin K?**

A. Fresh frozen plasma
B. Only vitamin K is needed.
C. Platelets
D. Prothrombin complex concentrate

27. **A 50-year-old patient presents with a large intracranial hemorrhage with evidence of herniation on the CT head. Which of the following is consistent with a diagnosis of brain death?**

A. Absent cerebral electrical activity on EEG except for rare focal epileptiform discharges overlying the region with the hemorrhage
B. Arrest of blood flow at the point of entry of the vessels to the dura on four-vessel catheter angiography
C. Minimal flow signal on transcranial Doppler
D. Lack of blink, pupillary, and gag reflexes with only rare breaths over the ventilator in an intubated patient

28. **Which of the following medications would be best for treating hyperactive delirium in an ICU setting?**

A. Midazolam
B. Dexmedetomidine
C. Propofol
D. Lorazepam

29. **Which of the following is *not* a risk factor used to calculate an intracerebral hemorrhage (ICH) score?**

A. Age
B. Hemorrhage volume
C. Location of the hemorrhage
D. Mass effect

30. **A 15-year-old boy was struck in the head by a baseball. He briefly lost consciousness when it occurred but then recovered. In the emergency department, he becomes confused and drowsy and then vomits repeatedly. Which of the following has most likely occurred?**

A. Aneurysmal rupture
B. Laceration of the middle meningeal artery
C. Post-traumatic seizure
D. Post-traumatic migraine

31. **Which of the following statements is *false*?**

A. Headgear usually does not prevent concussion in those playing sports but may help prevent more serious brain injury.
B. Loss of consciousness is required to diagnose concussion.
C. An athlete with a suspected concussion should be removed from play to prevent additional injury.
D. An apparently mild second head injury can be fatal if the patient has not recovered from the first head injury.

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**32. A boxer who has been repeatedly knocked out develops progressive cognitive decline. He has memory impairment and executive dysfunction. The symptoms began after retirement from the sport. MRI shows diffuse cerebral atrophy, a cavum septum pellucidum, and thinning of the corpus callosum. What is the most likely diagnosis?**

A. Chronic neurocognitive impairment
B. Chronic postconcussion syndrome
C. Chronic traumatic encephalopathy
D. Parkinson disease

**33. A 24-year-old patient was involved in a motor vehicle accident 5 days ago and is not awakening. Pupils are reactive, and corneal and gag reflexes are present. Withdrawal responses are symmetric. CT scans have been negative, and ICP is normal. What is the most likely MRI finding?**

A. A brainstem ischemic stroke
B. Microbleeds in the corpus callosum and at the gray–white junction
C. A subdural empyema
D. A subdural hygroma

**34. In the context of increased ICP and the Monro–Kellie hypothesis, which of the following is usually the most important blood volume regulator?**

A. Arteriolar oxygen
B. Arteriolar carbon dioxide
C. Arteriolar lactic acid
D. Venous oxygen

**35. Which of the following statements is *false*?**

A. Post-traumatic epilepsy is common after severe traumatic brain injury.
B. Administration of anti-seizure medications immediately after a traumatic brain injury prevents patients from developing epilepsy later.
C. Patients who develop epilepsy from a traumatic brain injury often do so within the first 2 years after the injury, but the onset can occur later.
D. Continuous EEG monitoring should be considered in patients with acute supratentorial brain injury and altered mental status.

**36. Mutism, lack of emotion, and minimal movement may indicate an injury to which region?**

A. Dorsolateral frontal lobe
B. Orbitofrontal region
C. Superior mesial frontal lobe
D. Inferior temporal lobe

**37. A 67-year-old man with a history of prostate cancer presents to the emergency department with lower back pain and leg weakness. MRI shows spinal metastases. What is the *first* step?**

A. Administer high-dose dexamethasone.
B. Arrange for spinal radiation therapy.
C. Make arrangements for surgery.
D. Order a CT myelogram to better define cord impingement.

**38. Which of the following statements is *false*?**

A. Patients with a traumatic spinal cord injury above the C5 level that is complete should be intubated.
B. A traumatic spinal cord injury in the upper thoracic spine that is complete typically causes early hypertension and tachycardia.
C. A common cause of spinal cord infarction is surgery, such as aortic surgery.
D. CSF drainage is used to treat acute spinal cord infarction.

**39. Which of the following features is not typical of metabolic encephalopathy?**

A. Nonreactive pupils
B. Nonfocal neurologic examination
C. Distractibility
D. Waxing and waning alertness

**40. The EEG finding of 14- and 6-Hz positive spikes is classically associated with which condition?**

A. Benzodiazepine intoxication
B. Cardiac arrest
C. Renal failure
D. Reye syndrome

**41. A 60-year-old man in the ICU develops altered mental status and has a brief seizure. He is afebrile. His complete blood count and CSF studies are unremarkable. His complete metabolic profile shows a sodium level of 115 mEq/L. Which of the following is most likely to prevent ongoing seizures?**

A. IV fosphenytoin load
B. IV levetiracetam load
C. Dose of IV lorazepam
D. Gradual sodium correction

**42. A patient who was admitted to the ICU with a frontal contusion becomes intermittently unresponsive. Laboratory studies are normal, and head CT findings are unchanged. Which of the following is most likely to yield the diagnosis?**

A. Continuous EEG monitoring
B. Repeat MRI
C. Magnetic resonance venography
D. Computed tomography angiography (CTA)

**43. A neurosurgical patient develops confusion. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is suspected. Which of the following is *least* likely to be present?**

A. Sodium level >145 mEq/L
B. Decreased urine output
C. Concentrated urine
D. Hypervolemia

**44. A patient in the ICU develops hemiballismus. Which of the following is the most likely etiology?**

A. Hypermagnesemia
B. Hypercalcemia
C. Hypomagnesemia
D. Nonketotic hyperglycemia

**45. A patient presents with leg weakness and areflexia. Electromyography (EMG) shows a demyelinating polyneuropathy. The weakness progresses to the upper extremities after admission. In addition to treating the patient's underlying condition, which of the following is recommended?**

A. Perform somatosensory evoked potentials (SSEPs).
B. Check forced vital capacity and negative inspiratory force.
C. Repeat EMG on the following day to assess for worsening.
D. Place a nasogastric tube.

**46. A patient with a history of respiratory failure and sepsis cannot move when the paralytic agent is discontinued. Creatine kinase is elevated. Muscle biopsy shows selective loss of myosin filaments. What is the most likely diagnosis?**

A. Critical illness myopathy
B. Critical illness polyneuropathy
C. Hypothyroidism
D. Periodic paralysis

**47. A 30-year-old man presents with respiratory failure. He is found to have limb–girdle weakness. EMG shows myotonic discharges in the paraspinal muscles. What is the most likely cause?**

A. Acid maltase deficiency
B. Myophosphorylase deficiency
C. Mutation in *PHOX2B*
D. Spinal muscular atrophy type 1 (Werdnig–Hoffman disease)

**48. Which of the following is a medication that should be avoided in patients with neuromuscular disease because of the risk of hyperkalemia?**

A. Atracurium
B. Succinylcholine
C. Rocuronium
D. Vecuronium

**49. What is Cushing's triad?**

A. Hypotension, bradycardia, apnea
B. Hypertension, tachycardia, apnea
C. Hypotension, tachycardia, tachypnea
D. Hypertension (widened pulse pressure), bradycardia, and irregular respirations

**50. If a patient has been treated with neuromuscular blocking agents, how can one best determine whether the agents are affecting the brain death examination?**

A. Check a serum level.
B. Perform the train-of-four technique with maximal ulnar stimulation.
C. Do an EMG.
D. Use a painful stimulus.

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# CRITICAL CARE AND TRAUMA

## ANSWERS

**1. B**

This is an example of vasogenic edema, which is associated with disruption of the blood–brain barrier.

Vasogenic edema is often seen in the setting of neoplastic lesions. Vasogenic edema is caused by an extracellular accumulation of fluid due to a disruption of the blood–brain barrier. This disruption results in extravasation of intravascular proteins and fluid into the interstitial space. The factors that mediate the extravasation of fluid include inflammatory mediators, endothelial permeability, hydrostatic forces, and the opening of tight junctions.

Interstitial edema can be seen in patients with obstructive hydrocephalus. Due to hydrostatic pressure, CSF is forced into the interstitial space from the ventricular spaces. This is also called transependymal edema.[1,2]

Cytotoxic edema is caused by intracellular fluid accumulation.[1] Cytotoxic edema is most commonly seen in hypoxic ischemia.

**2. A**

Cytotoxic edema is caused by changes in the cell membrane $Na^+/K^+$-ATPase pump, which cause fluid to accumulate in the cell. The blood–brain barrier is intact. Cytotoxic edema is commonly seen in hypoxia or ischemic injuries. Specifically, ischemia leads to the lack of energy in the cells, which leads to the depletion of ATP. This causes the $Na^+/K^+$-ATPase pump to fail, which affects the selective permeability of the cell membrane. Sodium accumulates in the cell, and water follows, resulting in swelling of the cell. There is increased signal on diffusion-weighted imaging due to restriction of water diffusion.

Vasogenic edema is related to disruption to the blood–brain barrier leading to extracellular fluid accumulation. There is movement of fluid and proteins from the intravascular space to the interstitial space.

Rapid onset of hyponatremia can result in cerebral edema due to the creation of an osmotic gradient that drives fluid into the cell. However, hypernatremia is not a cause for cerebral edema. Hypertonic saline is a treatment for cerebral edema.[1,2]

**3. A**

Patients who have suffered out-of-hospital cardiac arrest who have return of spontaneous circulation may benefit from targeted hypothermic therapy. Targeting a temperature of 32–34°C for 12–24 hours may decrease the risk of hypoxic ischemic brain damage. Temperatures lower than 32°C could be more harmful than beneficial. The risks associated with hypothermic therapy include arrythmias and systemic coagulopathy.[2,3] Hypothermia can also affect drug metabolism.

**4. A**

Rapid ascent into high altitudes can result in cerebral edema. This condition is characterized by fatigue, headache, insomnia, nausea, ataxia, and change in mental status. It can be potentially fatal. The rapid change in altitude can lead to hypoxia, resulting in the release of nitric oxide, free radicals, and cytokines. This leads to hypoxia-induced cerebral vasodilation with elevated capillary pressure and leakage, and eventually the disruption of the blood–brain barrier.[4]

Cardiac arrest can result in hypoxia, which can result in cerebral edema, but not coronary artery disease alone.[2]

Cerebral edema can occur in acute liver failure, but nonalcoholic fatty liver disease does not alone result in cerebral edema.

Acetazolamide is a treatment for idiopathic intracranial hypertension.

**5. A**

This patient has a skull base injury. The most common signs of a basilar skull fracture include dark bruising around the eyes (sometimes called raccoon eyes); CSF rhinorrhea; CSF otorrhea; bruising behind the ear over the mastoid process, also known as "Battle sign"; hemotympanum; and a scalp hematoma.[2] Basilar skull fractures can also cause pneumocephalus.

**6. D**

The normal ICP range is 5–15 mm Hg. Increased ICP is dangerous because it can cause a reduction in cerebral perfusion pressure that can result in ischemia. There are multiple ways to reduce ICP. Hyperventilation can be used to rapidly reduce ICP by decreasing the partial pressure of $CO_2$, which leads to cerebral vasoconstriction. This will reduce the cerebral blood volume, which in turn lowers the ICP. Hyperventilation is reserved for acute treatment. Prolonged hypocapnia can cause excessive vasoconstriction and ischemia.

Mannitol is an osmotic agent that lowers ICP by raising the serum osmolality and creating an osmotic gradient.

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It is not typical to administer as a continuous infusion because it can also cause hypotension; hypovolemia; and decreases in potassium, magnesium, and phosphorous.

Hypertonic saline is also an osmotic agent that can decrease ICP by creating an osmotic gradient.[5]

**7. D**

In a malignant MCA stroke, a patient would have suffered injury to >50% of the MCA territory, which increases the risk of edema and progression to midline shift and herniation. In malignant cerebral infarction, a stroke can affect the majority of the MCA territory and also encompass parts of the ACA and posterior cerebral artery territories. This large injury leads to space-occupying edema that causes increased ICP. The goal of hemicraniectomy in these patients is to have the brain herniate outward to decrease ICP and prevent intracranial herniation that can be life-threatening. Based on the DECIMAL, DESTINY, DESTINY II, HeADDFIRST, and HAMLET trials, it was determined that hemicraniectomy for malignant cerebral infarction led to higher survival rates but also increased disability. This was true both for patients younger than age 60 years and for those older than age 60 years. Ideally, this procedure should be performed within 48 hours of stroke onset in eligible patients.[6]

**8. C**

There are three factors that contribute the ICP waveform: P1, P2, and P3. P1 is the percussion wave, which represents arterial pulsation. P2 is the tidal wave, which represents intracranial compliance. P3 is the dicrotic wave, which represents the pressure transmitted by the closure of the aortic valve. CSF pressure is not directly represented in the ICP waveform.[7] (See Table 5.1.)

*Table 5.1* THE INTRACRANIAL PRESSURE WAVEFORMS

| INTRACRANIAL PRESSURE WAVEFORM | NAME OF THE WAVE | CAUSE OF THE WAVE |
|---|---|---|
| P1 | Percussion wave | Arterial pulsation |
| P2 | Tidal wave | Intracranial compliance |
| P3 | Dicrotic wave | Pressure transmitted by the closure of the aortic valve |

**9. C**

This patient is experiencing hyperactive delirium. Delirium is a consequence of acute encephalopathy. It can be associated with altered behavior, confusion, cognitive changes, psychomotor disturbance, and a change in sleep pattern. The psychomotor changes can be divided into three types: hyperactive delirium, hypoactive delirium, and mixed delirium.

Hyperactive delirium is characterized by restlessness, psychomotor agitation, changes in behavior, and sometimes hallucinations. This condition can at times resemble psychosis or mania.

Hypoactive delirium is characterized by excessive lethargy, psychomotor retardation, and decreased level of consciousness.

Mixed delirium can have fluctuating symptoms from both of the aforementioned types of delirium.

The most common causes of delirium include exposure to sedatives, analgesic medications, infections, electrolyte abnormalities, and acute metabolic derangements. Patients who have baseline dementia are at a higher risk for delirium.[8]

**10. D**

This patient has suffered a large ICH with midline shift that will likely continue to progress and cause herniation if not intervened upon. Intubation would be necessary if any neurosurgical intervention or monitoring is performed, and this patient does not wish to be intubated in the case of a medical emergency. A goals of care discussion should be arranged with the patient's power of attorney and their family, which can be mediated by the palliative care team. This patient's wishes should be respected, and comfort care should be provided.[9]

**11. C**

This patient is having rapidly progressive symptoms. It is important to remember the ABCs: airway, breathing, circulation. This patient has become obtunded and is unable to maintain his airway. Endotracheal intubation would be the first step in management.[9]

**12. D**

Reversible posterior leukoencephalopathy syndrome is also known as posterior reversible encephalopathy syndrome (PRES). This condition typically affects the white matter of the posterior aspects of the brain, but it can also involve other structures of the brain, including the mesial temporal lobes, basal ganglia, and even the parietal and frontal cortices. RPLS can be visualized on T1- and T2-weighed MRI images. It can be caused by elevated blood pressure, medications such as immunosuppressants, severe infection, kidney disease, and autoimmune processes. RPLS can occur in the setting of preeclampsia and eclampsia due to elevated blood pressures. Symptoms of this condition include altered mental status, seizures, headache, and sometimes visual impairment. Treatment includes blood pressure management, seizure management if seizures have occurred, potentially delivering the baby if the patient is experiencing preeclampsia or eclampsia, and removing contributing medications.[9]

**13. A**

Corticosteroids are used to treat cerebral edema that is a result of primary brain tumors or metastatic lesions to the brain. Dexamethasone is the most commonly used steroid for treating brain neoplasm-related edema. Steroids reduce inflammation caused by disruption of the blood–brain barrier. They are not indicated in RPLS, obstructive hydrocephalus, or ischemic stroke.[9]

**14. C**

Barbiturates decrease the brain's metabolic activity, which reduces the blood volume to the brain, resulting in lower ICP. Barbiturates can be used in intubated patients when the ICP has not responded to other medications and measures; they should not be the first treatment for increased ICP. If a patient is started on barbiturates for the purpose of achieving barbiturate coma to lower ICP, then the patient should be placed on continuous EEG monitoring. The goal is to see burst suppression on the EEG, which indicates that barbiturate coma has been achieved. Pentobarbital is the barbiturate that is most commonly used in this setting. Possible complications of barbiturate coma include hypotension, hypokalemia, respiratory complications, infection, hepatic dysfunction, and renal dysfunction.[5]

Propofol is a sedative agent that has a short half-life. This is useful in a critical care setting because it can be turned off quickly for neurologic exams. A possible complication of prolonged propofol use is propofol infusion syndrome, which is a potentially fatal condition associated with organ failure, hyperkalemia, metabolic and lactic acidosis, rhabdomyolysis, and hypertriglyceridemia.

**15. B**

A subdural hematoma is caused by tearing of the cortical bridging veins that drain into the dural venous sinuses. These vessels are very sensitive to sudden changes in velocity. The tearing of these vessels results in a collection of blood beneath the dura and above the arachnoid matter. A subdural hematoma can occur due to injury or can occur spontaneously. Brain atrophy is a risk factor for subdural hematoma.

Rupture of the middle meningeal artery results in an epidural hematoma.

Lipohyalinosis of the vessels is thought to be the mechanism of action for small-vessel disease.

Deposition of β-amyloid in the brain occurs in cerebral amyloid angiopathy, which can lead to lobar hemorrhages and cognitive decline.[9]

**16. C**

Status epilepticus is a neurologic emergency and is harmful to the brain. Early treatment of a seizure is imperative because the efficacy of medication decreases as seizure duration increases.

As in any medical emergency, it is important to first stabilize the patient. Check airway, breathing, and circulation. The first category of medications that should be administered to a patient having an active seizure, including status epilepticus, are benzodiazepines. Due to fast onset of action, lorazepam is often the first-line medication that is administered. Then a second-line agent should be administered, such as IV fosphenytoin, which can be infused faster than phenytoin, although the latter can still be used. Alternative second agents also include IV valproic acid, IV levetiracetam, or IV phenobarbital.

If seizures do not stop after the administration of a benzodiazepine and a second-line agent/anti-seizure medication, then the next step would be intubating the patient (if they are not already intubated) and then starting a propofol drip (in adults), midazolam drip, or pentobarbital. If propofol or midazolam is used and the seizures remain refractory to treatment, then the next step is placing the patient in a pentobarbital coma with the goal of burst suppression on EEG. Patients who are experiencing status epilepticus need to first be stabilized, but continuous EEG monitoring is very important in monitoring and managing these patients.[10]

**17. D**

Cerebral vasospasm is a major complication and is a major cause of neurologic morbidity after a SAH. This complication most often occurs in SAH due to aneurysmal bleeding. Vasospasm usually occurs between 3 and 15 days after the SAH. The symptoms of vasospasm include headache, nausea, vomiting, change in mental status, and focal neurologic changes. Diagnostic tools used to diagnose cerebral vasospasm include CT angiogram, digitally subtracted angiogram, and transcranial Doppler ultrasound. Rebleeding, hydrocephalus, and seizures are also complications of SAH. Rebleeding is an early complication that is most often seen within 72 hours of the initial SAH.[11]

**18. B**

Patients with SAH often state that they are having the worst headache of their life. The headache is sudden and severe. The patient might also have associated symptoms such as nausea, vomiting, photophobia, phonophobia, and neck stiffness. A patient with SAH may progress to coma or have focal neurologic deficits. The Hunt and Hess scale is a clinical scale designed to determine the severity of a SAH. Based on the Hunt and Hess grading scale, this patient would have a Hunt and Hess grade 4 SAH.[11–13] (See Box 5.1.)

*Box 5.1* **HUNT AND HESS GRADING SCALE**

Grade 0 = Unruptured aneurysm
Grade 1 = No symptoms or mild headache and minimal neck stiffness
Grade 2 = Moderate to severe headache, neck rigidity; no neurologic deficits (apart from cranial nerve palsy)
Grade 3 = Drowsy, confused, or mild focal deficit
Grade 4 = Stupor, hemiparesis
Grade 5 = Coma, decerebrate posturing

**19. C**

This patient has Guillain–Barré syndrome based on his symptoms and CSF. At this time, he is not showing any signs of imminent respiratory decompensation, although he should be closely monitored for this. The best option is to start treatment with IVIG, after checking an immunoglobulin A (IgA) level to rule out IgA deficiency.

High-dose corticosteroids are not indicated in Guillain–Barré syndrome. Acute rehabilitation would be beneficial after he has been treated with IVIG, but without treating the condition first, his weakness will progress despite physical therapy.[14]

**20. D**

This patient is experiencing serotonin syndrome as a result of taking multiple medications that increase serotonin levels. Tramadol is a pain medication that binds at the mu opioid receptors, but it also inhibits the reuptake of both norepinephrine and serotonin. Sertraline is a selective serotonin reuptake inhibitor. Amitriptyline is a tricyclic antidepressant that also inhibits the reuptake of both norepinephrine and serotonin. Last, trazodone is a serotonin receptor antagonist and reuptake inhibitor. All of these medications result in increased serum levels of serotonin, which can be dangerous if the level is too elevated.

Serotonin syndrome typically presents with a triad of symptoms that are encompassed by altered mental status, neuromuscular excitability, and autonomic symptoms. This can include confusion, agitation, restlessness, delirium, and coma; autonomic dysfunction such as hypertension, tachycardia, hyperthermia, nausea, and mydriasis; and neuromuscular changes such as tremor, clonus, hyperreflexia, and muscle rigidity. If not treated quickly, serotonin syndrome can result in rhabdomyolysis, metabolic acidosis, renal failure, seizures, respiratory failure, and even death. The treatment includes a combination of cyproheptadine, benzodiazepines, removal of the offending agent(s), and supportive care.[15]

Cholinergic crisis occurs when a patient is taking excessive quantities of acetylcholinesterase inhibitors, such as pyridostigmine. Symptoms include pinpoint pupils, increased secretions, diarrhea, bradycardia, muscle fasciculations, and weakness.

A myasthenic crisis occurs when a patient is experiencing acute worsening of their myasthenia gravis symptoms, which can include severe weakness, double vision, difficulty swallowing, and respiratory distress that can lead to respiratory failure.

Adrenergic crisis occurs when there is an increased serum level of catecholamines, which can lead to tachycardia, hyperthermia, diaphoresis, palpitations, altered mental status, change in behavior, and mydriasis.[9]

**21. A**

This patient is experiencing central pontine myelinolysis (CPM). This condition can occur after rapid correction of hyponatremia. The classic finding on MRI is symmetric signal intensity in the central pons, best seen on T2 fluid-attenuated inversion recovery imaging. This is caused by demyelination. Demyelinating changes are most often seen in the pons but can be seen in other parts of the brain as well. CPM symptoms can manifest between 3 and 10 days after a patient's hyponatremia is rapidly corrected. The symptoms include progressive weakness that can deteriorate into paraparesis or quadriparesis, dysphagia, dysarthria, altered mental status, lethargy, and pseudobulbar palsy. If the demyelination progresses to the ventral pons, then the patient can become "locked-in."[16]

Locked-in syndrome occurs in patients with injury to the ventral pons. In this condition, patients are awake and conscious, but they are quadriplegic and have bilateral facial paralysis, dysphagia, anarthria, and horizontal gaze palsy. The vertical gaze centers of the brain are spared, so the patients can move their eyes up and down. The ability to blink is also preserved. Patients with this condition might be able to communicate with vertical eye movements and blinking.

Damage to the mamillary bodies is seen in Wernicke–Korsakoff syndrome. These patients have agitation, hallucinations, severe memory loss with confabulation, and anterograde amnesia. This syndrome can be seen in patients who have severe thiamine deficiency, often seen in chronic, heavy alcohol users.

Damage to the bilateral thalami can be seen with a stroke involving the artery of Percheron. This can lead to vertical gaze palsy, agitation, cognitive changes, and coma.

**22. B**

This patient is suffering from a fat embolism. Fat embolism can occur due to trauma or surgery to long bones of the body such as the femur. Fat particles enter the bloodstream from the injured bone and then travel in the venous system to the lungs, causing respiratory symptoms. They can also enter into the arterial circulation, which can spread fat droplets systemically. Symptoms of fat embolism include respiratory distress, hypoxia, agitation, change in mental status, and coma. A petechial rash may be seen in the axillae, over the thorax, on the face, or involving the conjunctivae or oral mucosa. These fat emboli can travel to the brain and cause microhemorrhages, which can be seen on autopsy.[17]

**23. D**

This patient is experiencing neuroleptic malignant syndrome (NMS). NMS is caused by neuroleptic medications, most often antipsychotic medications. This condition is characterized by fever, muscle rigidity, autonomic dysfunction, and altered mental status. There can be many overlapping symptoms in NMS and serotonin syndrome. In NMS, the main feature is rigidity. The onset tends to be more gradual than in serotonin syndrome, and there is bradyreflexia in NMS. Fever can be seen in both conditions. Mydriasis is more common in serotonin syndrome.[9]

Treatment of NMS includes discontinuing the inciting agents and supportive care. Additional treatments include bromocriptine and dantrolene. Bromocriptine can increase serotonin centrally, so it should be avoided if serotonin syndrome has not been ruled out. Bromocriptine may worsen psychosis and may cause hypotension. Dantrolene inhibits intracellular calcium release. If dantrolene is given with calcium channel antagonists, the patient may experience cardiovascular collapse. Dantrolene can also cause hepatic toxicity. In addition to treating NMS, dantrolene has been used to treat malignant hyperthermia.

**24. C**

Nimodipine is a dihydropyridine voltage-gated calcium channel blocker that is administered after an aneurysmal SAH for vasospasm prophylaxis. It works as a vasodilator.

Clonidine, hydralazine, and amlodipine can help with elevated blood pressures but are less effective at preventing vasospasm.[18]

**25. D**

The Fisher grading scale for SAH is based on CT imaging of SAH. It is used to calculate the risk of vasospasm in an aneurysmal SAH based on the amount and distribution of blood. Fisher grade I means no SAH is seen. Grade II indicates that there is diffuse blood that is <1 mm thick vertically. Grade III is characterized by a localized clot and/or there is a vertical layer of blood ≥1 mm thick. Grade IV is defined as an intracerebral or intraventricular hemorrhage with diffuse or no SAH.

The Hunt and Hess grading scale is another tool used to measure the severity of SAH; this one is based on symptoms. Grade I equates to asymptomatic or minimal headache with slight nuchal rigidity. Grade II is characterized by moderate to severe headache with full nuchal rigidity. Grade III is associated with lethargy and/or confusion with mild focal neurologic deficits. Grade IV indicates that the patient is stuporous and has severe focal deficits such as hemiparesis. Grade V indicates that the patient is comatose with signs of severe neurologic impairment such as posturing.[18,19]

**26. D**

In patients who have ICH and an elevated INR due to warfarin use, multiple treatments are used in concert to reverse the bleeding. Prothrombin complex concentrate is used to rapidly correct the INR. It is a medication derived from clotting factor concentrates, which include factors II, VII, IX, and X. Prothrombin complex concentrate can be rapidly administered and can normalize the INR quickly. It works faster than fresh frozen plasma and vitamin K.

Fresh frozen plasma can be used to provide coagulation factors that are depleted by warfarin. It works quickly but can be associated with fluid overload, transfusion complications, and allergic reactions. In addition, it does not have a prolonged effect.

Vitamin K can reverse the effects of warfarin, but it takes a long time to reverse the INR because new clotting factors need to be synthesized.

Administering platelets will not have a significant effect on correcting an elevated INR.[20]

**27. B**

In 2023, the American Academy of Neurology (AAN) published an updated guideline on "Pediatric and Adult Brain Death/Death by Neurologic Criteria."[21] The article provides recommendations regarding general principles for the evaluation, qualifications to perform the evaluation, prerequisites for brain death determination, components of the brain death neurological examination, apnea testing as part of the evaluation, and special considerations for brain death determination.

The guideline states that a brain death evaluation should only be performed after a patient has sustained a "catastrophic, permanent brain injury" and the mechanism of brain injury is known to lead to brain death. Neuroimaging should be consistent with the mechanism of injury and severity of injury. Patients who have suffered brain death are expected to be comatose and to have no brainstem reflexes, including no respirations. Spinal cord reflexes, such as the triple flexion response, may be present in a patient with brain death.

Ancillary testing is not required if the patient can be declared brain dead based on clinical examination and apnea testing. It may be done if apnea testing or portions of the neurologic exam cannot be performed or cannot be interpreted. The guideline outlines when to and when not to do ancillary testing. For instance, ancillary testing can be done in patients with cervical spine injuries or in patients who would not tolerate apnea testing. It should *not* be performed in patients with hypothermia or high levels of sedating medications. Four-vessel catheter angiography can be used for ancillary testing. In patients with brain death, intracranial perfusion is absent. Radionucleotide perfusion scintigraphy may be used as an ancillary test. Transcranial Doppler ultrasonography may be used in adults but not children.

EEG, auditory evoked potentials (AEPs), SSEPs, CTA, and magnetic resonance angiography should *not* be used as ancillary tests to assist in the diagnosis of brain death. In this patient, epileptiform discharges on EEG indicate cortical activity and rule out brain death. In general, EEG does not evaluate brainstem function, so it is not recommended as an ancillary test per this guideline. Evoked potentials are not recommended in patients being evaluated for brain death; however, patients who have experienced brain death would not be expected to have waveforms after wave I on AEPs, a P100 waveform on visual evoked potential testing, or an N20 (cortical) waveform on SSEPs.

**28. B**

Dexmedetomidine can be used for the treatment of delirium because it has sedative, analgesic, and amnestic properties with less risk for respiratory depression. This medication does not need to be stopped for a patient to be awakened for a neurologic exam. It is an $\alpha_2$ receptor agonist. Side effects include bradycardia and hypotension.

Midazolam is a short-acting benzodiazepine that can cause sedation. Benzodiazepines are independently associated with the risk for delirium; however, they can be used judiciously for a delirious patient who is agitated. Propofol is not the first choice for treating ICU delirium.[9]

**29. D**

The ICH score is calculated based on the Glasgow Coma Scale (GCS) score and whether age is ≥80 years, ICH volume is ≥30 mL, there is intraventricular hemorrhage, or the hemorrhage is infratentorial in origin. Mass effect is not used to calculate the ICH score.[9]

**30. B**

Given his lucid interval, the most likely etiology is an epidural hematoma, which is most often caused by laceration of the middle meningeal artery. (See Figure 5.1.)

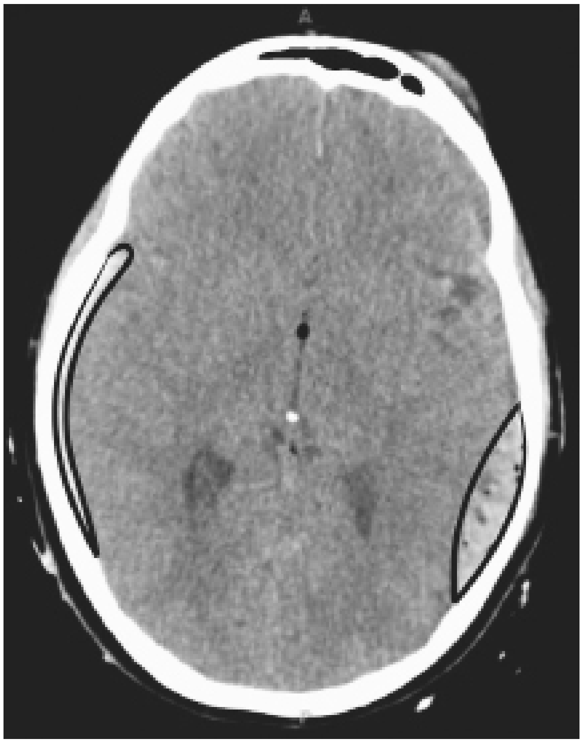

**Figure 5.1** A subdural hematoma is present on the right side of the brain (*left side of image*) and an epidural hematoma on the left side of the brain (*right side of image*). SOURCE: From Fisch A. *Neuroanatomy: Draw It to Know It*, 2nd ed., Fig. 2-2. New York: Oxford University Press; 2012.

Indications for head CT after a sports-related head injury include loss of consciousness, post-traumatic amnesia, GCS score <15, focal deficits, evidence of skull fracture, or clinical worsening.[22]

**31. B**

Loss of consciousness is *not* required to diagnose concussion. Headache is commonly reported. A patient with concussion commonly has anterograde or retrograde amnesia. Symptoms of concussion may not manifest immediately after the injury; they may appear later.

The sports with the greatest risk for head injury are football, rugby, lacrosse, ice hockey, and soccer.

A player with a suspected concussion should be removed from play to prevent additional injury. The player should be cleared by a licensed health care provider before returning to play. The AAN and the Centers for Disease Control and Prevention have created resources for coaches and health care providers who evaluate athletes. When the player returns to play, graded physical activity may be recommended.

If a player has a concussion, they need to be asymptomatic off medication before being cleared to return to play. A prior concussion is a risk factor for concussion. The term *second-impact syndrome* refers to massive brain edema after a second, apparently mild head injury that occurs when one is still recovering from a prior head injury.

Neuropsychological testing may help in decisions regarding return to play but is not required when a patient has had a concussion. If a player has had multiple concussions and reports cognitive impairment, neuropsychological testing may be helpful in deciding whether the player needs to retire from the sport.[22]

**32. C**

This patient has chronic traumatic encephalopathy (CTE). CTE is a neurodegenerative disease that is caused by repetitive traumatic brain injury. It may manifest with behavioral, motor, or cognitive signs or symptoms, and it is progressive. CTE tends to have a latency period, whereas chronic postconcussion syndrome does not. CTE is a tauopathy. There may be diffuse amyloid deposition or deposition of transactive response DNA binding protein 43 (TDP-43). Pathologic changes are seen in the superficial cortical layers, the perivascular regions, and the depths of sulci.

Chronic neurocognitive impairment typically follows multiple head injuries and is diagnosed with neuropsychological testing. It usually is not progressive.

Chronic postconcussion syndrome is diagnosed when a patient has postconcussive symptoms lasting longer than 1 year. It begins acutely after a single head injury. It usually is not progressive (Table 5.2).[23]

*Table 5.2* COMPARISON OF CHRONIC POSTCONCUSSION SYNDROME AND CHRONIC TRAUMATIC ENCEPHALOPATHY

| | CHRONIC POSTCONCUSSION SYNDROME | CHRONIC TRAUMATIC ENCEPHALOPATHY |
|---|---|---|
| Injury | Single | Repetitive |
| Latent period | No latent period | Latent period typically present |
| Progressive or not | Not progressive | Progressive |

**33. B**

This patient has diffuse axonal injury from a motor vehicle accident. This can cause microbleeds in the brainstem and corpus callosum and at the gray–white junction, which may not be seen on CT. MRI with gradient echo/susceptibility-weighted imaging/susceptibility-weighted angiography may be particularly helpful in detecting these lesions. At the microscopic level, axonal injury is manifested as axonal swellings (called retraction balls) in the white matter.

**34. B**

The Monro–Kellie hypothesis states that the sum of the brain, CSF, and intracranial blood volumes is constant. If there is a space-occupying lesion, the ICP increases. Typically, CSF volume decreases first in order to compensate. Also, venous blood may be pushed into the systemic circulation to compensate.

Cerebral perfusion pressure (CPP) is determined by the ICP and the mean arterial pressure (MAP): CPP = MAP − ICP.

The brain tries to maintain a certain amount of blood flow despite changes in perfusion pressure through cerebral autoregulation. Arterial carbon dioxide levels impact cerebral blood flow. Hypercapnia causes cerebral vasodilation and an increase in cerebral blood flow. Hypocapnia causes vasoconstriction and decreased cerebral blood flow.

The brain also tries to maintain a constant amount of oxygen delivery, so anemia, hemoglobin binding capacity problems, and severe hypoxia can raise cerebral blood flow. Acidosis can affect local flow.

In neurocritical care, the goal is to maintain adequate CPP, avoid excessive ICP, and avoid further brain injury.

**35. B**

Administration of anti-seizure medications immediately after a traumatic brain injury does *not* prevent patients from developing epilepsy later.[24–26]

Continuous EEG monitoring should be considered in patients with acute supratentorial brain injury and altered mental status due to the risk for nonconvulsive seizures.[27]

**36. C**

Mutism, lack of emotion, and minimal movement may indicate a lesion in the superior mesial frontal lobe.

**37. A**

Dexamethasone should be administered as soon as possible in a patient with spinal metastases and neurologic symptoms. Then further arrangements for treatment can be made.

**38. B**

A common cause of spinal cord infarction is surgery, such as aortic surgery. Most commonly, the thoracic cord is affected by spinal cord infarction. The goal of treatment of spinal cord ischemia is to increase cord perfusion. Vasopressors and lumbar CSF drainage have been used for this purpose. In general, corticosteroids are not recommended for spinal cord infarction.

In traumatic spinal cord injury, respiratory failure occurs with complete spinal cord lesions at C5 and above. These patients need to be intubated. Complete lesions of the upper thoracic spine interrupt supraspinal control of sympathetic preganglionic neurons in the thoracic cord. In the acute period, patients with major injury to the cord at the T6 level or above are at risk for neurogenic shock due to loss of control of the sympathetic nervous system and unopposed parasympathetic activity.[28] Neurogenic shock is characterized by bradycardia, hypotension, and skin that is warm and dry. Beyond the acute period, patients with cord lesions above T6 are at risk for autonomic dysreflexia. This is an exaggerated sympathetic response to stimuli below the level of the injury, such as constipation. Hypertension is the most common finding.[29]

Spinal shock is a transient condition characterized by urinary retention, bladder distention, and loss of reflexes (including the bulbocavernosus reflex) that occurs in the acute period after a traumatic spinal cord injury.[28]

Typically, cord injury needs to be bilateral to affect bowel, bladder, and sexual functions.

**39. A**

Typically, pupils are reactive in patients with metabolic encephalopathy. However, in severe metabolic encephalopathy, pupillary responses can be lost.

Usually, the examination is nonfocal; however, there may be focal findings in certain medical conditions, such as hypoglycemia and hyperglycemia.

**40. D**

The EEG finding of 14- and 6-Hz positive spikes is a normal variant. However, it is also associated with Reye syndrome.

**41. D**

This patient's altered mental status and seizure are caused by hyponatremia. Sodium correction is needed. However,

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overly rapid correction can cause CPM, which is also known as osmotic demyelination syndrome. Chronic hyponatremia requires even slower correction than acute hyponatremia.

**42. A**

Nonconvulsive status epilepticus is relatively common in the neurointensive care unit. The initial treatment is with a benzodiazepine such as lorazepam. Fluctuating consciousness should raise suspicion for this diagnosis. Prolonged EEG monitoring may be necessary to diagnose and manage this condition.

**43. A**

SIADH causes hyponatremia. Urine output is decreased, and the urine is concentrated. There is water retention, and the patient is hypervolemic.

Cerebral salt wasting is associated with laboratory results similar to those of SIADH and can occur in similar conditions (e.g., SAH, traumatic brain injury, and neurosurgery). Volume status helps differentiate the two conditions. Urine sodium is typically high in cerebral salt wasting. Patients with cerebral salt wasting need replacement of salt and water.

Diabetes insipidus (DI) is associated with hypernatremia, serum hyperosmolality, increased urine output, dilute urine, and hypovolemia. It may manifest as polyuria. There are many causes of DI, including brain tumor surgery, traumatic brain injury, and brain death. Central DI is treated with rehydration and desmopressin (DDAVP). Lithium can cause nephrogenic DI.

**44. D**

Nonketotic hyperglycemia (e.g., in patients with diabetes) can cause hemiballismus or hemichorea.[30] Increased signal is seen in the basal ganglia on T1-weighted MRI sequences.

Nonketotic hyperglycemia can also cause epilepsia partialis continua.

**45. B**

Given the progression of the weakness, the patient may be at risk for respiratory failure. The forced vital capacity and negative inspiratory force should be monitored closely.

There are specific clinical signs that indicate a patient may have respiratory decompensation. These signs include severe oropharyngeal weakness, bulbar weakness, autonomic dysfunction, progressive fatigue, vital capacity of less than 15 mL/kg, a decrease of more than 30% of the patient's baseline vital capacity, and partial pressure of oxygen <70.[14]

**46. A**

This patient has thick-filament myopathy, which is the most common type of critical illness myopathy. Risk factors include corticosteroids, neuromuscular blockers, and sepsis. There is selective loss of myosin filaments on muscle biopsy. Creatinine kinase may or may not be elevated in critical illness myopathy.

Critical illness polyneuropathy is an axonal sensorimotor polyneuropathy. Patients have sensory loss and generalized weakness that is worse distally than proximally. Risk factors include sepsis, multiorgan failure, respiratory failure, systemic inflammatory response syndrome, and persistently elevated blood glucose levels.

Hypothyroidism can cause a necrotizing myopathy, but the biopsy in this case is consistent with critical illness myopathy.

**47. A**

This patient has glycogen storage disease type II (GSD-II), or Pompe disease, which is caused by acid maltase deficiency, also known as acid α-glucosidase deficiency.

Infantile-onset Pompe disease manifests with cardiac failure, macroglossia, and hypotonia. Pompe disease can also manifest later in life with proximal muscle weakness and respiratory insufficiency. Creatinine kinase is elevated. EMG may show myotonic discharges in the paraspinal muscles. Enzyme replacement therapy is available.

Myophosphorylase deficiency causes GSD-V (McArdle disease), which leads to exercise intolerance.

Mutations in *PHOX2B* cause congenital central hypoventilation. *PHOX2B* is a homeobox gene that is important in the formation of the autonomic nervous system.

Spinal muscular atrophy type 1 (Werdnig–Hoffman disease) manifests in infancy with hypotonia, progressive weakness, and feeding difficulties. Respiratory failure occurs in early childhood if untreated.

**48. B**

Succinylcholine can cause hyperkalemia and arrhythmia in patients with neuromuscular disease or other causes of immobility. Chronic immobility leads to massive potassium release from depolarization when succinylcholine is administered.

The other agents are less likely to cause hyperkalemia, but their effect can be prolonged in patients with neuromuscular disease.

**49. D**

Cushing's triad is a late sign of intracranial hypertension. The triad is hypertension (widened pulse pressure), bradycardia, and irregular respirations. Patients may not manifest all three components.

**50. B**

If a patient has been treated with neuromuscular blocking agents, the train-of-four technique with maximal ulnar stimulation should be performed prior to a brain death examination.[21]

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# 6.

# DEMENTIA

## QUESTIONS

1. **A 60-year-old man is brought to clinic by his daughter. He has been forgetful and loses objects. She suspects dementia. Which of the following best differentiates mild cognitive impairment (MCI) from dementia?**
   A. Preservation of executive function
   B. Preservation of language skills
   C. Preservation of visuospatial skills
   D. Preservation of activities of daily living

2. **Which of the following is *not* an early finding in Alzheimer disease (AD)?**
   A. Episodic memory loss
   B. Rapid forgetting
   C. Difficulty managing finances
   D. Impaired procedural memory

3. **A college professor is concerned that he may have early Alzheimer disease. What is the most helpful evaluation?**
   A. Clinical Dementia Rating scale
   B. Mini-Mental State Examination
   C. Montreal Cognitive Assessment
   D. Neuropsychological testing

4. **A 60-year-old patient with a diagnosis of MCI is concerned about progression to Alzheimer disease. Which of the following is *not* an indicator of more rapid progression from MCI to Alzheimer disease (AD)?**
   A. Low $A\beta_{42}$ and high tau in cerebrospinal fluid (CSF)
   B. Carrier of $\varepsilon_4$ allele of apolipoprotein E
   C. Positron emission tomography (PET) shows hypometabolism in the frontal lobes
   D. A positive amyloid scan

5. **What is the greatest risk factor for AD?**
   A. Family history of AD
   B. Head trauma
   C. Socioeconomic status
   D. Increasing age

6. **A 50-year-old man presents with concerns about AD. His mother, maternal aunt, and maternal grandmother were diagnosed with AD. What is the most likely cause?**
   A. Mutation in *APP*
   B. Mutation in *ApoE4*
   C. Mutation in *PSEN1*
   D. Mutation in *PSEN2*

7. **In patients with AD, choline acetyltransferase is decreased in which structure?**
   A. Basalis nucleus of Meynert
   B. Raphe nuclei
   C. Nucleus accumbens
   D. Locus ceruleus

8. **Which of the following is *not* a characteristic pathologic finding in AD?**
   A. Synaptic loss
   B. Alzheimer type II astrocytes
   C. Granulovacuolar degeneration
   D. Hirano bodies

9. **Which of the following statements is *false*?**
   A. The diagnoses of AD and vascular cognitive impairment (VCI) are mutually exclusive.
   B. Depression may contribute to cognitive symptoms in patients who have had a stroke.
   C. VCI is typically subcortical in nature.
   D. VCI can occur without memory deficits.

10. **Which of the following is *not* recommended to prevent vascular cognitive impairment in at-risk individuals?**
    A. Antioxidants
    B. Mediterranean diet
    C. Physical activity
    D. Treatment of hypertension

11. **A 60-year-old, usually quiet college professor begins rolling her eyes when asked questions in class and yelling lewd comments at students. In the medical office, her examination is normal, but she is chewing on a pen. Which of the following diagnoses is the most likely?**
    A. Alzheimer disease
    B. Creutzfeldt–Jakob disease (CJD)
    C. Frontotemporal degeneration
    D. Progressive supranuclear palsy

12. **Which of the following is *least* consistent with behavioral variant frontotemporal degeneration (bvFTD)?**
    A. Apathy
    B. Loss of sympathy
    C. Ritualistic behavior
    D. Visuospatial difficulties

13. **Mutation in which of the following genes is the most common cause of familial frontotemporal dementia with amyotrophic lateral sclerosis (ALS)?**

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A. *C9ORF72*
B. *GRN*
C. *MAPT*
D. *SOD1*

**14. Which form of primary progressive aphasia (PPA) is most closely associated with AD?**

A. Semantic variant
B. Nonfluent/agrammatic variant
C. Logopenic variant (logopenic phonological aphasia)

**15. Which of the following statements is *false*?**

A. Attention difficulties and personality changes occur late in human immunodeficiency virus (HIV)-associated dementia.
B. HIV-associated dementia may respond to antiretroviral therapy.
C. Patients can develop HIV-associated neurocognitive disorders (HAND) even while receiving antiretroviral therapy.
D. Neuropsychological testing is required to diagnose milder forms of HIV-associated neurocognitive disorders.

**16. A patient is brought in by his family because of dementia. The family members report that he has poor attention, forgetfulness, visual hallucinations, depression, falls, and strange behavior in his sleep. On examination, he has facial masking and bradykinesia. There is no tremor. Which disease is the most likely cause?**

A. Alzheimer disease
B. Parkinson disease
C. Dementia with Lewy bodies (DLB)
D. Normal pressure hydrocephalus

**17. A 50-year-old patient presents with rapidly progressive cognitive problems and myoclonic jerks. Creutzfeldt-Jakob disease is suspected. Which of the following findings is *least* consistent with this diagnosis?**

A. Elevated CSF tau
B. Elevated CSF neuron-specific enolase
C. Increased signal in the basal ganglia on magnetic resonance imaging (MRI)
D. CSF pleocytosis

**18. Which of the following structures are most likely to be found in chronic traumatic encephalopathy (CTE)?**

A. Bunina bodies
B. Lewy bodies
C. Neurofibrillary tangles (NFTs)
D. Aggregates of ubiquitin

**19. Which sleep disorder is characteristic of older adults with dementia?**

A. Delayed sleep phase syndrome
B. Irregular sleep–wake rhythm disorder
C. Restless leg syndrome
D. Short sleeper

**20. Which of the following is *not* recommended for patients with dementia?**

A. Brief afternoon naps
B. Music therapy
C. Physical exercise
D. Social engagement

**21. Which of the following is *not* recommended to reduce behavioral symptoms in patients with dementia?**

A. Gently correct the patient each time the patient is mistaken.
B. Avoid changes in routine.
C. Avoid disturbing television programs and movies.
D. Prevent fatigue.

**22. Prior to objective testing with an on-the-road driving test, which of the following is most helpful in deciding whether a patient with dementia can drive safely?**

A. The Clinical Dementia Rating Scale
B. The patient thinks it is safe.
C. Neuropsychological testing
D. Analysis of processing speed

**23. A patient taking rivastigmine is having significant vomiting. The family believes that the medication has been beneficial, however. Which of the following drugs is recommended?**

A. Donepezil
B. Galantamine
C. Tacrine
D. Transdermal rivastigmine

**24. What is the mechanism of action for memantine?**

A. AMPA (α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate) receptor antagonist
B. Cholinesterase inhibitor
C. NMDA (*N*-methyl-ᴅ-aspartate) antagonist
D. Reduces glutamate release at the synapse

**25. What type of medication are lecanemab, aducanumab, and donanemab?**

A. Anti-α-synuclein antibodies
B. Anti-amyloid antibodies
C. Anti-phosphorylated tau antibodies
D. Anti-tau antibodies

**26. What is the most common sporadic atypical AD variant?**

A. Amnestic variant early onset AD
B. Corticobasal syndrome
C. Dysexecutive variant
D. Logopenic variant PPA
E. Posterior cortical atrophy (PCA)

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# DEMENTIA

## ANSWERS

**1. D**

Some cognitive changes are normal with aging, such as misplacing objects and difficulty multitasking. Patients with mild cognitive impairment (MCI) have true cognitive decline. They can have problems with memory, language, visuospatial skills, or executive function, but they have preserved function in daily life. Impaired function in activities of daily living indicates dementia. Patients with MCI do have an increased risk for AD compared with others their age.

Cardiovascular risk factors, including smoking, are risk factors for dementia. Physical, cognitive, and social activities may help delay cognitive decline.

In addition to cognitive screening, it is recommended that patients with suspected dementia undergo structural imaging, depression screening, and laboratory testing such as thyroid-stimulating hormone and vitamin $B_{12}$ levels.[1] Testing for neurosyphilis should also be considered.

**2. D**

Episodic memory loss and rapid forgetting occur early in the course of AD. (Episodic memory is memory for events.) Difficulty with finances may be another early sign.

Early impaired procedural memory is more characteristic of Parkinson disease. (Procedural memory is memory of how to perform tasks/skills, such as bike riding.) Patients with Parkinson disease and mutations in *GBA*, which encodes glucocerebrosidase, are at higher risk for dementia.[2] Pimavanserin, which is a serotonin 2A/2C antagonist/inverse agonist, is approved by the U.S. Food and Drug Administration for the treatment of psychosis in Parkinson patients. Antipsychotics that reduce dopaminergic activity can worsen motor symptoms in Parkinson disease. In addition, antipsychotics increase the risk for cerebrovascular events in the elderly and increase the risk for death in patients with dementia.

**3. D**

In a highly educated individual, neuropsychological testing is the most helpful instrument for detecting early dementia.[3]

**4. C**

Hypometabolism in the temporal and parietal lobes is consistent with a more rapid progression from MCI to AD (Table 6.1).[4]

*Table 6.1* **INDICATORS OF MORE RAPID PROGRESSION FROM MILD COGNITIVE IMPAIRMENT TO ALZHEIMER DISEASE**

| TYPE OF INFORMATION | FINDING |
|---|---|
| **Clinical** | **More severe clinical impairment** |
| **Cerebrospinal fluid** | **Low $A\beta_{42}$, elevated tau, and phosphorylated tau** |
| **Genetic** | **Carrier of $\varepsilon_4$ allele of apolipoprotein E** |
| **Magnetic resonance imaging** | **Atrophic hippocampi** |
| **SPECT/PET** | **Hypometabolism in temporal and parietal lobes, positive amyloid scan** |

PET, positron emission tomography; SPECT, single-photon emission computed tomography.

**5. D**

Increasing age is the primary risk factor for AD. After age, the greatest risk factor is a positive family history.

The major factor contributing to the development of sporadic AD is the presence of the $\varepsilon_4$ allele of apolipoprotein E.

Women have almost twice the lifetime risk for AD compared to men.[1]

**6. C**

Mutations in the genes encoding amyloid-β A4 precursor protein, presenilin 1, and presenilin 2 cause autosomal dominant AD.

Mutations in presenilin 1 are the most common cause of familial AD. They cause early onset of symptoms. *PSEN1*, which encodes presenilin 1, is located on chromosome 14.

Mutations in *APP* are the second most common cause of familial AD. The *APP* gene, which encodes amyloid precursor protein, is located on chromosome 21. Mutations in *APP* can also cause some familial forms of cerebral amyloid angiopathy.

*PSEN2*, which encodes presenilin 2, is located on chromosome 1. Patients with *PSEN2* mutations have the oldest age at onset among the familial forms of AD, but the age at onset is variable.

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*ApoE4* encodes apolipoprotein E and is located on chromosome 19. The apolipoprotein E $\varepsilon_4$ allele usually causes late-onset AD. Having two copies of this allele increases the risk for younger age at onset.

7. **A**

In patients with AD, choline acetyltransferase is decreased in the basalis nucleus of Meynert.

8. **B**

Alzheimer type II astrocytes are not found in AD. They occur in hyperammonemia.

AD cannot be diagnosed definitively without pathology results. Neuropathologic features of AD include granulovacuolar degeneration, Hirano bodies, senile/neuritic plaques, NFTs, neuronal death, synaptic loss, and brain atrophy. Senile plaques consist of amyloid and neuritic processes. The major component of NFTs is tau protein, which is abnormally phosphorylated microtubule-associated protein. AD is a type of tauopathy.

9. **A**

Alzheimer disease and vascular cognitive impairment can co-occur.

Vascular cognitive impairment (VCI) is usually associated with subcortical symptoms. Cognitive slowing and abulia are more common than memory problems. Patients with VCI may just have executive function deficits. There is no specific cognitive profile that is diagnostic of VCI; patients with VCI can have any type of neuropsychological dysfunction. Micro-infarcts and white matter disease are thought to contribute more to VCI than macro-infarcts and large-vessel disease.

Depression is one of the most common psychiatric conditions after stroke and needs to be ruled out in patients with cognitive impairment.

10. **A**

Treatment of cardiovascular risk factors is recommended to prevent VCI. A Mediterranean diet and physical activity may help prevent cognitive decline. Antioxidants have not been proven to be helpful.

The American Heart Association/American Stroke Association guideline from 2011 regarding vascular contributions to cognitive impairment stated that donepezil can be used to improve cognition in vascular dementia and that galantamine may be helpful for patients with mixed AD and vascular dementia.[5]

11. **C**

This patient has behavioral variant frontotemporal degeneration (bvFTD), which is the most common frontotemporal dementia syndrome. Selective serotonin reuptake inhibitors have been used to treat behaviors in these patients.[6] Venlafaxine (a serotonin norepinephrine reuptake inhibitor), trazodone, and atypical antipsychotics have also been used.[6,7] Cholinesterase inhibitors and memantine are usually not effective in this condition.[7]

12. **D**

Patients with bvFTD have disinhibition, which is often evident by socially inappropriate behaviors. Patients have a change in personality. They become apathetic and lose the ability to empathize and sympathize. Hyperorality, dietary changes, and obsessive–compulsive behaviors are seen. Neuropsychological testing indicates executive deficits. Memory and visuospatial functions are relatively spared. Frontal and/or anterior temporal atrophy, hypoperfusion, or hypometabolism support the diagnosis.

Genes that cause bvFTD include *MAPT*, *GRN*, and *C9ORF72*. Mutations in *MAPT* cause hyperphosphorylated tau deposition; mutations in *GRN* and *C9ORF72* cause deposition of the 43-kDa transactive response (TAR) DNA binding protein (TDP-43). A smaller group of patients have inclusions containing the fused in sarcoma (FUS) protein. Both the *MAPT* and *GRN* genes are located on chromosome 17q21. Mutations in *GRN* (also known as *PGRN*), which encodes granulin, can also cause nonfluent variant primary progressive aphasia and neuronal ceroid lipofuscinosis-11 (CLN11). Psychosis can occur in patients with bvFTD caused by mutations in *C9ORF72* (chromosome 9, open reading frame 72).

Progressive supranuclear palsy and corticobasal syndrome can manifest with symptoms similar to those of bvFTD.

13. **A**

ALS can occur with any of the types of FTD, but it is most common in patients with bvFTD. Expansion of a GGGGCC hexanucleotide repeat in the noncoding region of the gene *C9ORF72* on chromosome 9 causes familial FTD and/or ALS.

The gene *SOD1* encodes superoxide dismutase-1. Mutations in the SOD1 protein can also cause ALS.

(The genes *MAPT* and *GRN* are discussed in question 12.)

14. **C**

There are three types of primary progressive aphasia (PPA): logopenic, semantic, and nonfluent/agrammatic variants. All are associated with impaired naming.

The logopenic variant is most closely associated with AD. Patients with the logopenic variant of PPA have word-finding difficulties in conversational speech and have particular difficulty with repetition.[8] Single-word comprehension is intact. There is atrophy at the left temporoparietal junction.

The semantic variant and the nonfluent/agrammatic variant are associated with FTD. (See Table 6.2.)

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*Table 6.2* COMPARISON OF THE PRIMARY PROGRESSIVE APHASIAS

| | LOGOPENIC VARIANT | SEMANTIC VARIANT | NONFLUENT/AGRAMMATIC VARIANT |
|---|---|---|---|
| Speech deficits | Word-finding problems, difficulty with sentence repetition | Fluent aphasia with<br>Anomia<br>Difficulty comprehending single words<br>Difficulty with confrontation naming | Impaired grammar, able to repeat |
| Disease with which it is most closely associated | Alzheimer disease | Frontotemporal dementia | Frontotemporal dementia |
| Location of atrophy | Left temporoparietal junction | Anterior temporal lobes, usually left more than right | Left perisylvian region |

The semantic variant of PPA affects the anterior temporal lobes, usually left more than right.[9] Patients have a fluent aphasia with anomia. They have difficulty with confrontation naming (e.g., naming pictures of objects) and difficulty comprehending single words. Aggregates of TDP-43 are most commonly found on neuropathology.[8]

The nonfluent/agrammatic variant of PPA is associated with left perisylvian atrophy. Impaired grammar produces nonfluent speech. Tau-positive neuronal and glial inclusions are most commonly found on neuropathology, but TDP-43 has also been found. Mutations in the *GRN* gene can cause this variant.

Speech therapy is recommended for patients with PPA.

A neuropsychological test that helps to differentiate PPA from amnestic dementia is the Three Words–Three Shapes Test, which can assess nonverbal visual memory. In PPA, nonverbal episodic memory is more intact.[3]

**15. A**

HIV-associated neurocognitive disorders include HIV-associated dementia, HIV-associated mild neurocognitive disorder, and HIV-associated asymptomatic neurocognitive impairment. HAND can occur at any stage of HIV infection and can occur despite treatment.

HIV-associated dementia is the most common neurologic condition in patients with AIDS and may be the presenting symptom. HIV-associated dementia is a subcortical dementia. Attention difficulties and personality changes occur early.

Neuropsychological testing is required to diagnose milder forms of HIV-associated neurocognitive disorders. Patients with mild neurocognitive disorder have mildly impaired function and deficits in at least two cognitive domains. The diagnosis of asymptomatic neurocognitive disorder also requires deficits in two cognitive domains. These patients have no difficulties with everyday activities.

If a patient has HAND, the physician may want to consider the central nervous system penetration effectiveness of the patient's medications. Efavirenz tends to cause neuropsychiatric side effects.[10] Therefore, it is not ideal for patients with HIV-associated dementia.

**16. C**

This patient has DLB. Dementia is a prerequisite for the diagnosis of DLB. Other core features are fluctuations in cognition, especially attention and alertness; visual hallucinations; and parkinsonism. Patients with DLB can have bradykinesia, facial masking, and rigidity, similar to patients with Parkinson disease, but resting tremor is unusual. Suggestive features of DLB are rapid eye movement sleep behavior disorder, neuroleptic sensitivity, and low dopamine transporter uptake in the basal ganglia on single-photon emission computed tomography or PET. Cholinesterase inhibitors have been used to treat DLB. Symptomatic treatment may also be necessary. Traditional neuroleptics are avoided because of neuroleptic sensitivity. Dopamine agonists can worsen psychiatric symptoms in patients with DLB.[11] Iodine-123 metaiodobenzylguanidine (MIBG) myocardial scintigraphy has been used to try to differentiate dementia from DLB from AD. MIBG is a measure of postganglionic sympathetic cardiac innervation. It is more likely to be reduced in DLB than AD.[12]

Normal pressure hydrocephalus can cause dementia and a gait disorder, but facial masking does not occur.

**17. D**

Cerebrospinal fluid pleocytosis is rare in CJD and should raise suspicion for another etiology.

American Academy of Neurology guidelines have recommended checking for the presence of 14-3-3 protein in the CSF if a patient has rapidly progressing dementia of unknown etiology and there is strong suspicion of sporadic CJD.[13] Patients with CJD may also have elevated levels of tau, P-tau, and neuron-specific enolase in the CSF. The real-time quaking-induced conversion assay, which measures abnormal prion protein ($PrP^{Sc}$), is another test for sporadic CJD.

Patients with sporadic CJD may have increased signal in the basal ganglia and/or cortical ribbon on fluid-attenuated inversion recovery MRI and diffusion-weighted imaging sequences. Periodic sharp wave complexes occurring every 0.5 to 1 seconds are characteristic of sporadic CJD. Patients with variant CJD have increased signal in the pulvinar and do not have periodic sharp wave complexes.

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**18. C**

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease that is caused by repetitive traumatic brain injury. It is a 3R and 4R tauopathy. Hyperphosphorylated tau accumulates in neurons and astrocytes. NFTs and neuritic threads are seen. Abnormal TDP-43 is often present in CTE. Abnormal axonal pathology is also seen.[14]

Although it is a tauopathy, there are some neuropathologic features of CTE that separate it from AD and other tauopathies. In CTE, there are perivascular collections of neuronal NFTs.[15] Also, NFTs in CTE tend to start in the depths of the sulci in the frontal cortex.[15,16] Rather than being found in layers IV and V, as in patients with AD, NFTs are found in the superficial layers (II and III) in patients with CTE.[14]

Dementia pugilistica is a type of CTE. It is a severe dementia caused by brain injury sustained during a boxing career.

The term *post-traumatic dementia* refers to dementia resulting from a single traumatic brain injury.

Bunina bodies are inclusions found in patients with ALS.

**19. B**

Older adults with dementia often have irregular sleep–wake rhythm disorder, which is characterized by loss of a normal circadian rhythm. The patient awakens and sleeps at variable times, naps intermittently during the day, and does not sleep for long periods.

A short sleeper is one who routinely sleeps less than 6 hours per night but functions normally and has no complaints of sleepiness. It is a normal variant.

**20. A**

Brief afternoon naps may disrupt sleep at night and are not recommended for patients with dementia. It is recommended that patients with dementia be screened for sleep disorders.[1]

**21. A**

Avoiding confrontation, unless safety is an issue, helps reduce behavioral symptoms. Changes in routine should be avoided whenever possible.

If behavioral symptoms are not severe, they may respond to treatment of the dementia. Antipsychotics increase the risk for cerebrovascular events in the elderly and for death in patients with dementia. There are caregiver training programs to teach caregivers how to prevent and handle behavioral symptoms.

**22. A**

According to American Academy of Neurology guidelines, the Clinical Dementia Rating Scale may be used to help determine whether a patient can drive safely. The fact that a patient believes their driving is safe does not predict safety. If a patient reports concern about driving, then there should be increased concern about the patient's ability to drive. If a caregiver thinks that the patient's driving is unsafe, the physician should be concerned that it is unsafe for the patient to drive. Motor vehicle accidents, reduced mileage driven, aggression, and impulsivity also raise concern that driving is unsafe. A Mini-Mental State Examination score of 24 or less is also concerning.[17]

**23. D**

The patient's medication can be changed to transdermal rivastigmine, which should reduce the vomiting.

Rivastigmine is a pseudo-irreversible cholinesterase inhibitor (acetylcholinesterase and butyrylcholinesterase). Donepezil, galantamine, and tacrine are also cholinesterase inhibitors.

Galantamine is a reversible, competitive acetylcholinesterase inhibitor and an allosteric nicotinic receptor modulator. Tacrine must be given four times per day and causes hepatotoxicity; therefore, the other medications are preferred. Cholinesterase inhibitors can cause symptoms related to the parasympathetic nervous system. They can cause nausea, vomiting, diarrhea, anorexia, and weight loss. Bradycardia and syncope can also occur. In addition, donepezil can be associated with rhabdomyolysis and vivid dreams.[1]

**24. C**

Memantine is a noncompetitive NMDA receptor antagonist. It can cause constipation, headache, dizziness, and flu-like symptoms.[1]

**25. B**

Lecanemab, aducanumab, and donanemab are anti-amyloid antibodies, which are thought to remove β-amyloid from the brain. They have a risk for antibody-related imaging abnormalities (ARIA), including edema and hemorrhage.

**26. A**

Amnestic variant early onset AD is the most common sporadic atypical AD variant. It is associated with early progressive memory loss. It impacts attention, language, visual–spatial skills, and executive function.

Behavioral variant AD resembles bvFTD; however, delusions and hallucinations are more likely in behavioral variant AD.

Corticobasal syndrome associated with AD (motor variant AD) clinically resembles corticobasal syndrome–corticobasal degeneration.

Dysexecutive variant is associated with difficulties with organization and multitasking.

Most cases of logopenic variant PPA are due to AD. Patients with language variant AD/logopenic variant PPA have word-finding problems, phonemic paraphasias (mispronunciation of words), and difficulties with sentence repetition.

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Most cases of PCA are due to AD. PCA is also known as the visual–spatial variant of AD. Patients may have Balint syndrome, Gerstmann syndrome, limb apraxia, constructional apraxia, alexia, or visual field defects. PCA has been subdivided into dorsal, ventral, and caudal variants depending on the symptomatology. Early symptoms may include difficulties driving.[18] See Box 6.1.

### *Box 6.1* TYPES OF SPORADIC ATYPICAL ALZHEIMER DISEASE VARIANTS

- Amnestic variant early onset Alzheimer disease
- Behavioral variant Alzheimer disease
- Corticobasal syndrome
- Dysexecutive variant
- Logopenic variant primary progressive aphasia
- Posterior cortical atrophy

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# 7.

# DEMYELINATING DISEASES AND NEUROIMMUNOLOGY

## QUESTIONS

1. **A 25-year-old woman presents with eye pain and blurry vision. On examination, she has decreased visual acuity and an afferent pupillary defect. Brain magnetic resonance imaging (MRI) is normal apart from the eye. What is the treatment of choice?**
   A. Intravenous methylprednisolone followed by an oral prednisone taper
   B. Oral prednisone alone
   C. Therapeutic lumbar puncture
   D. Interferon-β

2. **A patient presents with painless vision loss in one eye. He is found to have a centrocecal scotoma in that eye. His mother and brother experienced similar symptoms and eventually lost vision in both eyes. The patient's brain MRI is normal. Methylprednisolone does not improve his symptoms. What is the most likely diagnosis?**
   A. Optic neuritis
   B. Leber hereditary optic neuropathy
   C. Myotonic dystrophy type 1
   D. Oculopharyngeal muscular dystrophy

3. **A patient involved in a motor vehicle accident has a brain MRI. Lesions consistent with multiple sclerosis (MS) are seen. The patient is asymptomatic from the lesions. What is the patient's diagnosis?**
   A. Clinically isolated syndrome (CIS)
   B. Possible MS
   C. Probable MS
   D. Radiographically isolated syndrome (RIS)

4. **Which of the following statements is *false*?**
   A. MS can be diagnosed at the time of presentation of a CIS if the appropriate MRI findings are seen.
   B. A single MRI scan can demonstrate dissemination in time.
   C. Oligoclonal bands are pathognomonic of MS.
   D. In a patient with MS, brainstem symptoms at initial presentation suggest a worse prognosis.

5. **Which of the following statements about MS is true?**
   A. MS is more common in identical twins than in fraternal twins.
   B. MS has been linked to a polymorphism in the major histocompatibility class II locus on chromosome 6p.
   C. Geography affects the risk for MS.
   D. All of the above.

6. **Which of the following is most likely to be seen in a patient with MS?**
   A. Complete external ophthalmoplegia
   B. Complete third nerve palsy
   C. Sixth nerve palsy
   D. Vertical gaze palsy

7. **Which of the following is most likely to be seen in a patient with MS?**
   A. Diabetes insipidus
   B. Facial myokymia
   C. Livedo reticularis
   D. Retinopathy

8. **Which of the following can be diagnosed with MS?**
   A. A patient with at least two clinical attacks and clinical evidence of at least two lesions
   B. A patient with at least two clinical attacks, clinical evidence of one lesion, and evidence of a prior attack in a different anatomical location
   C. A patient with one clinical attack and clinical evidence of at least two lesions
   D. A and B

9. **A patient presents with headache, an abducens palsy, and pyramidal signs. She has a long history of mucosal ulcers and uveitis. What is the most likely diagnosis?**
   A. Behçet disease
   B. MS
   C. Neurosarcoidosis
   D. Whipple disease

10. **Which of the following is most likely to be seen in a patient with MS?**
    A. Extrapyramidal signs
    B. Myorhythmia
    C. Simultaneous enhancement of all the brain lesions
    D. Open ring sign

11. **Which of the following is *least* likely to occur in MS?**
    A. Depression
    B. Vitamin D deficiency
    C. Sexual dysfunction
    D. Seizures

12. **Which of the following is most abundant in an active MS plaque?**
    A. B cells
    B. Neutrophils
    C. Eosinophils
    D. T cells

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**13. Which of the following is the most specific characteristic of an active MS plaque?**

A. Macrophages containing myelin debris
B. Astrocytic fibrillary gliosis
C. Almost no oligodendrocytes
D. Sharp margins on gross specimens

**14. What are shadow plaques?**

A. MS plaques with significant axon loss
B. Smaller MS plaques adjacent to a larger plaque
C. MS plaques with significant vasogenic edema
D. Remyelinating MS plaques

**15. Which of the following is *least* likely to cause reappearance of prior deficits in a patient with MS?**

A. Exercise
B. Fever
C. Pregnancy
D. Urinary tract infection

**16. A young woman with relapsing remitting multiple sclerosis (RRMS) asks about having a child. Which of the following statements is *false*?**

A. There is a decrease in the relapse rate during pregnancy.
B. There is an increased risk for miscarriage in RRMS.
C. In most patients with RRMS, there is no increase in delivery complications.
D. RRMS does *not* cause an increase in birth defects.
E. Multiple courses of corticosteroids during pregnancy are associated with low birth weight.

**17. Which treatment for MS is safest during pregnancy?**

A. Fingolimod
B. Glatiramer acetate
C. Dalfampridine
D. Natalizumab

**18. Which medication for MS is most likely to cause fetal toxicity?**

A. Dimethyl fumarate
B. Mitoxantrone
C. Rituximab
D. Teriflunomide

**19. What is the reason for treating an MS exacerbation with methylprednisolone?**

A. Prevention of future MS attacks
B. To delay the next MS attack
C. More rapid improvement of symptoms
D. Reduction in the likelihood of permanent injury from an MS lesion

**20. A patient presents with an MS exacerbation. Which of the following statements is *false*?**

A. Randomized controlled trials support the use of methylprednisolone to treat acute MS exacerbations in children.
B. Methylprednisolone can cause gastrointestinal bleeding.
C. Plasma exchange is a second-line treatment for adults with MS relapses, but it can be associated with cardiac arrhythmias.
D. Intravenous immunoglobulin (IVIG) can be used for acute MS exacerbations in adults if steroids are contraindicated.
E. IVIG has a risk for aseptic meningitis.

**21. Which of the following is the most likely to occur in a patient taking interferon?**

A. Anemia
B. Flu-like symptoms
C. Leukopenia
D. Thrombocytopenia

**22. Which of the following medications is contraindicated in patients with poor kidney function (i.e., a low glomerular filtration rate)?**

A. Dalfampridine
B. Fingolimod
C. Natalizumab
D. Teriflunomide

**23. Which of the following medications is a sphingosine-1-phosphate (S1P) receptor modulator?**

A. Dalfampridine
B. Fingolimod
C. Ocrelizumab
D. Teriflunomide

**24. Which of the following medications is associated with cardiac arrhythmias, elevated liver enzymes, macular edema, skin cancer, and herpesvirus infections?**

A. Cyclophosphamide
B. Fingolimod
C. Rituximab
D. Mitoxantrone

**25. What is the mechanism of action of natalizumab?**

A. It is an S1P receptor agonist.
B. It interferes with the interaction between very late antigen-4 and vascular endothelial adhesion molecule-1.
C. It is an antibody to CD20.
D. It inhibits dihydroorotate dehydrogenase.

**26. Which of the following statements is *false*?**

A. Mitoxantrone is a chemotherapeutic agent that decreases lymphocyte proliferation.
B. There is a limit for mitoxantrone dosing that should not be exceeded in a patient's lifetime.
C. There is a black box warning for mitoxantrone because of cardiotoxicity and treatment-associated leukemia.
D. If cardiotoxicity occurs with mitoxantrone, it occurs during the first months of treatment.

**27. A patient who has been doing well on natalizumab presents with changes in behavior, gradually worsening left-sided weakness, and seizures. Which condition needs to be ruled out?**

A. Progressive multifocal leukoencephalopathy (PML)
B. Immune reconstitution inflammatory syndrome
C. Hepatic encephalopathy
D. Reversible posterior leukoencephalopathy

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**28. A patient presents with vision impairment, hearing loss, and headache. MRI demonstrates lesions in the middle of the corpus callosum. She also has lacunar infarcts. Branch retinal artery occlusions are seen with retinal fluorescein angiography. What is the most likely diagnosis?**

A. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
B. MS
C. Neurosarcoidosis
D. Susac syndrome
E. Autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy

**29. Which of the following medications is a monoclonal antibody to CD52 and may carry a high risk for autoimmune complications?**

A. Alemtuzumab
B. Daclizumab
C. Ocrelizumab
D. Tocilizumab

**30. A 30-year-old woman is diagnosed with an asymmetric partial transverse myelitis (TM). An inflammatory etiology is suspected. What is the first-line treatment?**

A. Interferon-β
B. IVIG
C. Methylprednisolone
D. Plasma exchange

**31. True or false?**

A patient with TM and positive antinuclear antibodies (ANAs) is presumed to have a rheumatologic cause for their TM.

**32. A 20-year-old woman is diagnosed with TM. Which of the following findings suggests that neuromyelitis optica spectrum disorder (NMOSD), *not* MS, is the etiology?**

A. The presence of oligoclonal bands
B. Longitudinally extensive TM (i.e., the lesion involves at least three vertebral segments)
C. Involvement of only the dorsolateral cord
D. Involvement of less than one-third of the cross-sectional area of the cord

**33. The presence of which of the following suggests that NMOSD is the etiology of TM?**

A. Aquaporin-4 antibodies
B. Myelin basic protein antibodies
C. Proteolipid protein antibodies
D. Elevated immunoglobulin G (IgG) index

**34. A 14-year-old girl presents with right arm weakness after an upper respiratory tract infection. MRI shows asymmetric lesions that have increased signal on T2-weighted and fluid-attenuated inversion recovery sequences in the cortical gray–white junction of both hemispheres, in the deep white matter, and in the thalami and basal ganglia. There is relative sparing of the periventricular white matter. Cognition is normal. What is her diagnosis?**

A. CIS
B. MS
C. Acute disseminated encephalomyelitis (monophasic)
D. Acute disseminated encephalomyelitis (multiphasic)

**35. Which of the following statements is *false*?**

A. In children, most cases of acute TM are idiopathic, whereas in adults, a minority of cases are idiopathic.
B. In children, acute TM is more commonly associated with MS if *fewer* than three vertebral segments are involved.
C. Methylprednisolone is the treatment of choice for idiopathic acute TM in children.
D. Infants have a better prognosis than other children with acute TM.

**36. True or false?**

NMOSD can manifest with intractable hiccups, vomiting, or narcolepsy.

**37. What is the target for neuromyelitis optica immunoglobulin G (NMO-IgG)?**

A. A water channel protein
B. A sodium channel
C. A potassium channel
D. A calcium channel

**38. Where is the target for NMO-IgG?**

A. On astrocytes
B. On oligodendrocytes
C. On ependymal cells
D. On the myelin sheath

**39. Which of the following potential treatments used for NMOSD is an anti-CD20 monoclonal antibody?**

A. Aquaporumab
B. Eculizumab
C. Rituximab
D. Tocilizumab

**40. Thiopurine methyltransferase levels are checked before NMOSD is treated with which agent?**

A. Aquaporumab
B. Azathioprine
C. Mycophenolate mofetil
D. Tocilizumab

**41. A 10-year-old girl presents with headache, sleepiness, and difficulty walking. She was normal until 2 weeks ago, when she had a virus with fever. MRI shows multiple lesions in the cerebral white matter, thalamus, and basal ganglia. Most of the lesions enhance. Analysis of the cerebrospinal fluid (CSF) shows 30 white blood cells (98% lymphocytes). Oligoclonal bands are negative. What is the most likely diagnosis?**

A. Acute cerebellar ataxia
B. Acute disseminated encephalomyelitis (ADEM)
C. MS
D. Devic disease

**42. Which of the following is *least* typical of ADEM?**

A. Severe axonal loss
B. Perivenular demyelination
C. The presence of lymphocytes around the veins
D. The presence of macrophages around the veins

**43. What was the first medication approved by the U.S. Food and Drug Administration (FDA) for primary progressive MS?**

A. Cladribine
B. Eculizumab
C. Fingolimod
D. Ocrelizumab
E. Siponimod

**44. Which of the following should be avoided in NMOSD?**

A. Azathioprine
B. Interferon-β
C. Mycophenolate
D. Rituximab

**45. Which of the following statements regarding demyelinating disorders in children is *false*?**

A. The presence of hypointense lesions on T1-weighted MRI is more suggestive of ADEM than of MS.
B. Periventricular lesions are more consistent with MS than with ADEM.
C. During childhood, MS usually follows a relapsing remitting course.
D. Children with MS tend to have a higher rate of relapse than adults with MS.
E. Children with MS tend to have more inflammation than adults.

**46. Which of the following antibodies have been found in some patients with chronic relapsing inflammatory optic neuropathy and in some patients with ADEM who have prominent optic nerve involvement?**

A. Antibodies to GD1a
B. Antibodies to myelin-associated glycoprotein (MAG)
C. Antibodies to myelin oligodendrocyte glycoprotein (MOG)
D. Antibodies to sulfatide
E. Antibodies to collapsin response-mediating protein-associated (CRMP-5)

**47. A 25-year-old woman with a recent upper respiratory tract infection presents with fever, confusion, and seizures. The C-reactive protein level is elevated. MRI shows diffuse, bilateral asymmetric lesions in the cerebral white matter. There is edema surrounding the lesions, and some of the lesions enhance. Some of the enhancing lesions are C-shaped. Susceptibility-weighted images show multiple punctate hemorrhages in the gray and white matter. She has a CSF pleocytosis. She subsequently becomes comatose and dies. What is the most likely diagnosis?**

A. Acute hemorrhagic leukoencephalitis
B. Embolic stroke
C. Malignant MS (Marburg disease)
D. Marchiafava–Bignami disease

**48. Which of the following causes an ADEM-like illness but is also associated with hepatosplenomegaly, lymphadenopathy, and increased levels of serum ferritin and triglycerides?**

A. Cerebrotendinous xanthomatosis
B. Fabry disease
C. Macrophage activation syndrome
D. Metachromatic leukodystrophy
E. POLR3-related leukodystrophy

**49. Which of the following cells are cytotoxic and kill cells infected with viruses?**

A. $CD4^+$ T cells
B. $CD8^+$ T cells
C. Gemistocytes
D. Natural killer cells

**50. True or false?**

Remyelination occurs more quickly in the peripheral nervous system than in the central nervous system (CNS).

**51. Which of the following is found in CNS myelin?**

A. Proteolipid protein (PLP)
B. Peripheral myelin protein 22 (PMP-22)
C. Myelin protein zero (MPZ)

**52. Patients with myasthenia gravis (MG) who test negative for acetylcholine receptor antibodies may have which of the following antibodies?**

A. Anti-GQ1b antibodies
B. Anti-GM1 antibodies
C. Anti-MAG antibodies
D. Anti-MuSK antibodies

**53. Patients with MG with which of these antibodies often have a thymoma?**

A. Anti-striated muscle antibodies
B. Anti-GQ1b antibodies
C. Anti-MAG antibodies
D. Anti-Hu antibodies

**54. Which of the following features is *least* consistent with the diagnosis of PML?**

A. Areas of demyelination
B. Extensive perivascular cuffing and necrosis
C. Large astrocytes with bizarre nuclei
D. Oligodendrocytes with intranuclear inclusions

**55. Fill in the blank: Before giving human IVIG, it is recommended that the __________________ level be checked.**

A. Albumin
B. IgA
C. IgE
D. IgG

**56. A patient presents with limbic encephalitis and neuromyotonia. Morvan syndrome is suspected. Which**

**of the following conditions is most closely associated with Morvan syndrome?**

A. Breast cancer
B. Malignant thymoma
C. Small-cell lung cancer
D. Thyroid carcinoma

**57. A 9-year-old boy presents with intractable focal clonic seizures of the left hand and arm. His left hand and arm are becoming progressively weaker. CSF analysis demonstrates no infection. MRI shows atrophy of the right hemisphere. Which of the following antibodies are most likely to be present?**

A. Antibodies to the calcium channel
B. Antibodies to the γ-aminobutyric acid A ($GABA_A$) receptor
C. Antibodies to the glutamate receptor 3
D. Antibodies to the sodium channel

**58. A patient has antibodies to MOG. Which of the following is *least* likely to be the patient's clinical presentation?**

A. Area postrema syndrome
B. Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS)
C. Focal encephalitis
D. Myelitis
E. Progressive leukodystrophy

**59. A patient with mental status changes and abnormal movements is suspected to have anti–*N*-methyl-D-aspartate (NMDA) receptor encephalitis. Which of the following statements is *false*?**

A. MRI of the brain may be normal in patients with anti-NMDA receptor encephalitis.
B. Females with GFAP astrocytopathy are at risk for the same tumor as females with anti-NMDA receptor encephalitis.
C. Herpes simplex virus encephalitis is a trigger of NMDA receptor autoimmunity.
D. Treatment decisions should be based on antibody titers.
E. Extreme delta brushes can be seen on electroencephalography (EEG) in some patients with anti-NMDA receptor encephalitis.

**60. Which of the following antibodies are most often associated with multifocal motor neuropathy?**

A. Monoclonal anti-MAG antibodies
B. Monoclonal anti-GM1 antibodies
C. Polyclonal anti-GM1 antibodies
D. Polyclonal anti-GQ1b antibodies

**61. A mutation in which of the following genes is *least* likely to cause abnormal white matter?**

A. *EIF2B1*
B. *GALC*
C. *SCN9A*
D. *TREX1*
E. *TUBB4A*

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# DEMYELINATING DISEASES AND NEUROIMMUNOLOGY

## ANSWERS

**1. A**

This patient has optic neuritis (see Box 7.1). The treatment of choice is methylprednisolone followed by prednisone according to the Optic Neuritis Treatment Trial.[1]

Brain MRI at the time of diagnosis with optic neuritis does help predict the risk for MS. There is not enough information to warrant the diagnosis of MS or initiation of treatment with interferon-β in this patient.

**Box 7.1 FEATURES OF OPTIC NEURITIS**

- It is painful.
- A relative afferent pupillary defect is present.
- Decreased contrast and color vision are often found.
- The optic disc may appear swollen.
- The patient may see light flashes with eye movements.
- It is usually unilateral but may be bilateral.
- Retinal hemorrhage and retinal exudates are unusual.
- MRI of the orbits can be normal.[2]

It is rare to have complete vision loss with optic neuritis due to MS.

Severe vision loss and lack of response to steroids raise concern for neuromyelitis optica spectrum disorder (NMOSD). NMOSD also tends to cause simultaneous bilateral optic neuritis, to involve the chiasm, and to cause an altitudinal visual field defect.[3] NMOSD may co-occur with systemic autoimmune disorders.

**2. B**

This patient and his family members have Leber hereditary optic neuropathy. This is a mitochondrial disorder that demonstrates maternal inheritance and is more common in males than in females. Patients initially develop unilateral symptoms and then progress to bilateral severe vision loss. This disease does not respond to methylprednisolone. It can be associated with cardiac conduction defects. Idebenone, a benzoquinone, has been used to treat Leber hereditary optic neuropathy.

Oculopharyngeal muscular dystrophy causes ptosis but does not cause vision loss. It is associated with an expansion of a GCN trinucleotide repeat in the gene *PABPN1*.

The most common ophthalmologic findings in myotonic dystrophy type 1 are ptosis and cataracts.

The strong inheritance pattern and severe vision loss in the patient's family members make optic neuritis less likely.

**3. D**

This patient has radiographically isolated syndrome (RIS). Patients with RIS have MRI findings suggestive of MS that are found incidentally, without any clinical symptoms consistent with the disease.

Cervical cord lesions indicate increased risk for clinical conversion from RIS to MS.

**4. C**

The 2017 revised McDonald criteria are used for the diagnosis of MS. The diagnosis of MS requires dissemination in time and space. A single MRI scan can demonstrate dissemination in time if there are both asymptomatic gadolinium-enhancing and non-enhancing lesions. A single MRI scan can also demonstrate dissemination in space if there are T2-weighted lesions in two of four characteristic locations for MS (i.e., periventricular, juxtacortical/cortical, infratentorial, and spinal cord) (see Boxes 7.2 and 7.3).[4]

**Box 7.2 CHARACTERISTIC LOCATIONS OF MS LESIONS USED FOR DISSEMINATION OF SPACE CRITERIA**

- Periventricular
- Juxtacortical/cortical
- Infratentorial
- Spinal cord

**Box 7.3 CHANGES IN THE 2017 MCDONALD CRITERIA[4,5]**

- Patients with clinically isolated syndrome and dissemination in space can be diagnosed with MS if CSF-specific oligoclonal bands are present; oligoclonal bands can be used to substitute for evidence of dissemination in time.
- Symptomatic supratentorial, infratentorial, and spinal cord lesions (but not optic nerve lesions) can be used to indicate dissemination in space or dissemination in time.
- Previously, a symptomatic brainstem or spinal cord lesion in a patient with clinically isolated syndrome could not be used as evidence of dissemination in space or dissemination in time.
- Cortical lesions can be used to indicate dissemination in space.

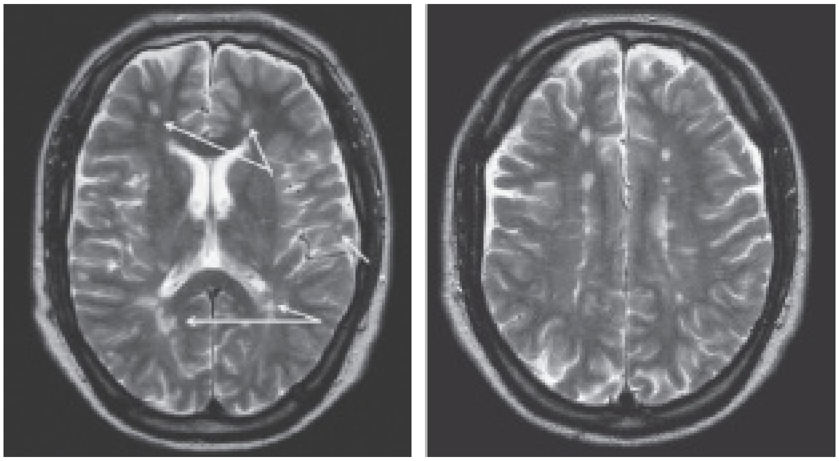

**Figure 7.1** T2-weighted MRI scan showing white matter lesions (*arrows*) in a distribution typical of MS. SOURCE: From Scolding N, Wilkins A. *ONL Multiple Sclerosis*, Fig. 4.1. New York: Oxford University Press; 2012.

A positive CSF result is defined as the presence of oligoclonal bands in the CSF (but not in the serum) or an elevated CSF IgG index.

Although oligoclonal bands are common in patients with MS, they are also found in other conditions. For example, oligoclonal bands can be seen in CNS infections such as subacute sclerosing panencephalitis, herpes encephalitis, neurosyphilis, and Lyme disease. They can also be seen in neurosarcoidosis, cerebral lupus, and stroke.

The temporal profiles seen in MS are relapsing remitting MS (RRMS), secondary progressive MS (SPMS), and primary progressive MS. RRMS is the most common type and has the least severe clinical course.

Motor, brainstem, or bowel/bladder symptoms with the initial attack suggest a worse prognosis. Also, failure to recover completely from the first attack suggests a worse prognosis (see Figure 7.1).[6]

## 5. D

Twin studies indicate a genetic component: MS is more common among identical twins than fraternal twins. Also, first-degree relatives of patients with MS have an increased risk for the disease, but there is not a Mendelian inheritance pattern.

MS susceptibility has been linked to polymorphisms in the DR gene, particularly *DRB1*1501.*

MS is less common near the equator. It is more common in northern latitudes. There is some evidence that vitamin D deficiency plays a role in this difference in prevalence. Low sunlight exposure is also a risk factor for MS. Other risk factors for MS include obesity, smoking, and Ebstein–Barr virus seropositivity.[7]

## 6. C

Sixth nerve palsy and unilateral or bilateral internuclear ophthalmoplegia are typical in MS. One-and-a-half syndrome is less common but can occur in MS.

Complete external ophthalmoplegia, a complete third nerve palsy, and vertical gaze palsies are *not* typical for MS.

Complete external ophthalmoplegia is found in mitochondrial DNA deletion syndromes such as chronic progressive external ophthalmoplegia, Kearns–Sayre syndrome, and Pearson syndrome. It is also seen in some *POLG*-related disorders.

## 7. B

Facial myokymia can be seen in patients with MS, but the other conditions are atypical for MS and suggest that there may be another diagnosis.

Sarcoidosis, histiocytosis, and NMOSD are mimickers of MS that can cause diabetes insipidus and other hypothalamic disturbances. Bone lesions occur in histiocytosis.

Lupus and antiphospholipid antibody syndrome are mimickers of MS that can cause livedo reticularis.

Retinopathy occurs in mitochondrial diseases and Susac syndrome, which can resemble MS.

## 8. D

The patient with one clinical attack and clinical evidence of at least two lesions needs CSF-specific oligoclonal bands, another clinical attack, or evidence of dissemination in time (DIT) based on MRI.

A patient with one clinical attack and clinical evidence of one lesion needs evidence of dissemination in space (DIS) and evidence of DIT. DIS could be demonstrated with MRI or another clinical attack involving a different anatomic site. DIT criteria could be met by CSF-specific oligoclonal bands, another clinical attack, or evidence of DIT based on MRI.[4]

## 9. A

Patients with MS may have a history of uveitis, but this constellation of symptoms is most consistent with Behçet disease, which can mimic MS. Behçet disease is a type of vasculitis associated with recurrent oral and genital ulcers, uveitis, and skin lesions. It can affect multiple systems. In the CNS, Behçet disease can cause cerebral venous thrombosis or parenchymal involvement. It can cause recurrent meningoencephalitis, cranial nerve palsies, ataxia, and pyramidal signs. Brain MRI may show diffuse white matter involvement, infiltrating brainstem lesions, or atrophy of the brainstem.[8] Features that help to differentiate Behçet disease from MS may include increased neutrophils in the CSF and positive HLA-B51.[9]

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is another disease that affects the brainstem and resembles MS. It can cause diplopia and ataxia. The characteristic MRI finding is enhancing punctate lesions in the pons.[10]

Neurosarcoidosis can cause cranial neuropathies particularly of the facial nerve.

Sarcoidosis can also cause neuropsychiatric symptoms, hydrocephalus, meningitis, focal leptomeningeal disease, periventricular white matter lesions, hypothalamic–pituitary dysfunction (e.g., diabetes insipidus), and myelopathy. In patients with spinal cord sarcoidosis, spine MRI may show dorsal subpial enhancement. Enhancement of the central canal and dorsal subpial region can create a trident pattern on axial images.[11] The patient may have an elevated concentration of angiotensin-converting enzyme. Hypercalcemia can occur. Lung involvement and conjunctival biopsy can aid in the diagnosis of neurosarcoidosis. Thoracic MRI may show swelling of lymph nodes at the carina or hilum.[11] Sarcoid is associated with noncaseating granulomas and multinucleated giant cells.

**10. D**

Extrapyramidal signs are atypical for MS and raise concern for MS mimickers such as Whipple disease and Wilson disease. Whipple disease can cause oculomasticatory myorhythmia. Palatal tremor (palatal myoclonus) can occur in MS.

Simultaneous enhancement of all the brain lesions can be seen in vasculitis, lymphoma, and sarcoidosis. Sarcoidosis can also cause meningeal enhancement and lesions with persistent enhancement on MRI with gadolinium.

**11. D**

Seizures can occur in patients with MS but are not common. Seizures can occur in mimickers of MS, such as Whipple disease. Dementia is also a red flag that MS might not be the diagnosis.[12]

Depression, vitamin D deficiency, and sexual dysfunction are common in MS. Fatigue, spasticity, and bladder problems are also common issues. Pain may also need to be addressed.

**12. D**

T cells are the most abundant cells in an active MS plaque.

**13. A**

In an active MS plaque, there are perivascular and parenchymal lymphocytes and macrophages. There are also reactive astrocytes and macrophages containing myelin debris. Astrocytes become gemistocytes, which are plump cells with abundant fibrillary processes. Most inflammation is at the edge of the lesion. T cells are seen there.

Chronic plaques are characterized by astrocytic fibrillary gliosis and sharp margins on gross specimens. Almost no oligodendrocytes are present.

**14. D**

Shadow plaques are plaques where remyelination is occurring. They contain remyelinating axons, which have thin myelination.

**15. C**

The terms pseudoexacerbation and pseudorelapse refer to worsening of MS symptoms rather than progression of disease. Exercise, fever, and illness can cause pseudoexacerbation/pseudorelapse.

**16. B**

RRMS does *not* increase the risk of miscarriage, delivery complications, or birth defects.

There is a lower risk for an MS exacerbation during pregnancy, but there is a higher risk in the postpartum period.

**17. B**

Of the medications listed, glatiramer acetate (Copaxone) is the safest in pregnancy. It consists of a polymer that includes salt forms of four amino acids (L-glutamic acid, L-lysine, L-alanine, and L-tyrosine). It is administered by injection, and some patients have an immediate postinjection reaction. Lipoatrophy can occur with extended use.

**18. D**

Teriflunomide is pregnancy category X. Teriflunomide reversibly inhibits dihydroorotate dehydrogenase, which results in decreased proliferation of autoreactive T cells. Teriflunomide reduces progression of disability. It can cause diarrhea and hepatotoxicity. It potentially could reactivate tuberculosis. Initially, it can cause hair thinning. Clearance of teriflunomide takes months. There is an accelerated elimination procedure.

Mitoxantrone is pregnancy category D.

Rituximab and dimethyl fumarate are pregnancy category C. Dimethyl fumarate is taken orally twice daily and can cause flushing, vomiting, diarrhea, and abdominal pain.

**19. C**

Methylprednisolone produces more rapid clinical improvement, but it does not affect the long-term course of MS.

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**20. A**

There are no randomized controlled trials of the use of methylprednisolone in children with MS exacerbations.

Corticosteroids can cause avascular necrosis, ulcers, osteoporosis, hyperglycemia, mood disturbances, and insomnia.

**21. B**

Injection site reactions, flu-like symptoms, elevated liver enzymes, and neutralizing antibodies can occur in patients taking interferon.

**22. A**

Dalfampridine (Ampyra) is the extended-release form of 4-aminopyridine, which is a potassium channel blocker. It improves ambulation. Dalfampridine is contraindicated in patients with poor kidney function due to seizure risk.

**23. B**

Fingolimod (Gilenya) is an sphingosine-1-phosphate receptor modulator. An active metabolite of fingolimod binds to sphingosine 1-phosphate receptors 1, 3, 4, and 5.[13] Siponimod and ozanimod are also sphingosine-1-phosphate receptor modulators, but they bind to fewer receptors. All three medications prevent egression of lymphocytes from lymphoid tissues.

Siponimod is a selective sphingosine 1-phosphate (S1P) receptor modulator; it binds to S1P receptors 1 and 5. It was the "first disease-modifying therapy proven to reduce disability progression, cognitive decline and total brain volume loss versus placebo in patients with typical SPMS."[14]

Like siponimod, ozanimod binds to S1P receptors 1 and 5. An active metabolite of ozanimod inhibits monoamine oxidase B in vitro; therefore, the package insert warns about interactions with monoamine oxidase inhibitors and adrenergic and serotonergic medications.[15]

**24. B**

Fingolimod has been associated with cardiac arrhythmias, elevated liver enzymes, macular edema, skin cancer, and herpesvirus infections. Electrocardiographic monitoring is recommended during the first administration of fingolimod, which can cause bradycardia or atrioventricular conduction delay.

Fingolimod was the first medication approved by the FDA for pediatric MS (age 10 years or older).[13]

Cyclophosphamide is an alkylating agent. Side effects can include emesis, bladder cancer, and transient myelosuppression.[16]

**25. B**

Natalizumab is an antibody to $\alpha_4$ integrin. It interferes with the interaction between the integrin very late antigen-4 and vascular endothelial adhesion molecule-1. Natalizumab prevents adhesion and thereby prevents entry of lymphocytes into the CNS.

**26. D**

A maximum cumulative dose of mitoxantrone for a patient's lifetime has been determined. Mitoxantrone can cause acute myeloid leukemia and cardiotoxicity. In addition to checking cardiac function before initiating treatment and before each dose, the FDA has recommended annual cardiac function evaluations after completion of mitoxantrone therapy because there can be delayed cardiotoxicity. Cardiac toxicity is manifested as decreased left ventricular ejection fraction and/or congestive heart failure.[17]

**27. A**

This patient has symptoms that are concerning for PML. PML can cause subacute, progressive symptoms such as seizures, aphasia, hemiparesis, behavior changes, and retrochiasmal visual deficits. PML progresses over several weeks, rather than having a more acute onset, as seen in MS. Unlike MS, PML usually does not affect the optic nerves or spinal cord.

If a patient develops PML while taking natalizumab, the drug should be permanently discontinued. Patients who are HIV positive, have an immune disorder, or have a hematologic malignant condition should not be given natalizumab. Natalizumab should not be combined with immunosuppressants. A washout period is recommended before starting natalizumab if the patient has been taking an immunosuppressant. Patients who are seronegative for anti-JC virus antibodies are at lower risk for PML (see Box 7.4).[18]

### *Box 7.4* RISK FACTORS FOR DEVELOPMENT OF PML IN PATIENTS TAKING NATALIZUMAB

- Antibodies to the JC virus
- Treatment with natalizumab for longer than 2 years
- Prior treatment with immunosuppressants

PML associated with natalizumab responds differently than other types of PML in regard to immune reconstitution. Immune function can be restored more quickly in patients with natalizumab-related PML. Immune reconstitution inflammatory syndrome can occur in patients with PML due to natalizumab when natalizumab is discontinued.

**28. D**

This patient has Susac syndrome, which can mimic MS. Susac syndrome is a microangiopathy/immune-mediated endotheliopathy (autoimmune response to endothelial cells).[19,20] Susac syndrome affects the brain, retina, and cochlea, causing a triad of encephalopathy, vision loss, and sensorineural hearing loss. Focal neurologic signs, tinnitus, or vertigo may be present. Patients may have scotoma due to optic involvement. Branch retinal artery occlusions can be seen with retinal fluorescein angiography. On brain MRI, abnormalities can be seen in the white matter, especially the corpus callosum, as well as in the leptomeninges and gray matter.[20] Susac syndrome causes lesions in the middle of the corpus callosum; the periphery of the corpus callosum tends to be spared. This helps differentiate it from MS. Corpus callosum lesions in Susac syndrome have been described as "snowballs" that evolve into "holes." The internal capsule may show microinfarcts in a "string of pearls" pattern.[20] Lesions can also be found in the basal ganglia. Initial treatment of Susac treatment is with corticosteroids and IVIG. [20]

Autoimmune glial fibrillary acidic protein astrocytopathy is an inflammatory disorder that affects the CNS, often causing meningoencephalomyelitis. It can also cause blurred vision. It can be associated with optic nerve papillitis and optic disc edema.[2] It is diagnosed with antibodies to GFAP in the CSF. Patients also have evidence of CSF inflammation, such as elevated lymphocytes, elevated protein, or oligoclonal bands. T1 images with contrast may show enhancement, for instance, in a radial periventricular pattern. It is often steroid-responsive. Some patients have teratoma.[21]

**29. A**

Alemtuzumab is a monoclonal antibody to CD52 that depletes mature lymphocytes and monocytes. Alemtuzumab carries a risk for autoimmune complications such as immune thrombocytopenic purpura, autoimmune thyroiditis, and glomerular nephropathy. It increases one's risk for malignancy. It can also cause an infusion reaction.

Daclizumab is an anti-interleukin-2 (IL-2) receptor antibody; specifically, it is an antibody to CD25.

Ocrelizumab is an anti-CD20 antibody.

Tocilizumab is an anti-IL-6 receptor antibody (see Tables 7.1 and 7.2).

**30. C**

Methylprednisolone is the first-line treatment to improve symptoms of TM.

**31. False**

ANAs can be found in patients with NMOSD and in patients with MS.

**32. B**

Transverse myelitis that is longitudinally extensive (i.e., involving at least three vertebral segments) is more consistent with NMOSD than with MS. A complete spinal cord syndrome and centrally located lesions also raise suspicion for NMOSD. Paroxysmal tonic spasms can occur in myelitis patients with NMOSD. Oligoclonal bands are more likely to occur in patients with MS than patients with NMOSD. Patients with NMOSD are more likely to have pleocytosis, with neutrophilic or eosinophilic predominance, than patients with MS. Also, patients with NMOSD may have an elevated GFAP level.[16]

*Table 7.1* MECHANISM OF ACTION OF MULTIPLE SCLEROSIS MEDICATIONS

| MEDICATION | MECHANISM OF ACTION |
|---|---|
| Alemtuzumab (Lemtrada) | Monoclonal antibody to CD52; decreases proliferation of autoreactive T cells |
| 4-aminopyridine/ dalfampridine (Ampyra) | Potassium channel blocker |
| Cladribine (Leustatin injection, Mavenclad tablets) | Synthetic purine anti-metabolite (interferes with DNA synthesis and repair) |
| Cyclophosphamide | Alkylating agent |
| Dimethyl fumarate (Tecfidera) | Alkylating agent, unclear mechanism, activates erythroid 2-related factor 2 (Nrf2) pathway[22] |
| Fingolimod (Gilenya) | Sphingosine-1-phosphate receptor modulator; prevents lymphocytes from leaving lymph node |
| Glatiramer acetate (Copaxone, Glatopa) | Immunomodulation, synthetic mimic of myelin basic protein |
| Interferon-β 1a (Avonex, Rebif); Peginterferon-β 1a (Plegridy) | Inhibits proinflammatory cytokines |
| Interferon-β 1b (Betaseron, Extavia) | Inhibits proinflammatory cytokines |
| Mitoxantrone (Novantrone) | Decreases lymphocyte proliferation, type II topoisomerase inhibitor[16] |
| Natalizumab (Tysabri) | Antibody to $\alpha_4$ integrin; prevents entry of lymphocytes into the central nervous system |
| Ocrelizumab (Ocrevus) | Anti-CD20 monoclonal antibody |
| Ofatumumab (Kesimpta) | Anti-CD20 monoclonal antibody |
| Ozanimod (Zeposia) | Sphingosine 1-phosphate receptor modulator; prevents lymphocytes from leaving lymph node |
| Siponimod (Mayzent) | Sphingosine 1-phosphate receptor modulator; prevents lymphocytes from leaving lymph node |
| Teriflunomide (Aubagio) | Inhibits dihydroorotate dehydrogenase; decreases proliferation of autoreactive T cells |

In addition to oligoclonal bands, other red flags that TM is *not* due to NMOSD include onset less than 4 hours, a chronic progressive course, and cerebral lesions that enhance for more than 3 months.[16]

The TM lesions in patients with MS tend to be more patchy, more peripheral, and shorter in length. MS cord lesions are usually less than two vertebral segments in length, involve less than half of the cross-sectional area, and most often involve the dorsolateral cord.

*Table 7.2* ROUTE OF ADMINISTRATION OF MULTIPLE SCLEROSIS MEDICATIONS

| MEDICATION | ROUTE OF ADMINISTRATION |
|---|---|
| Alemtuzumab (Lemtrada) | Infusion |
| 4-Aminopyridine/dalfampridine (Ampyra) | Oral |
| Cladribine (Mavenclad) | Oral |
| Cladribine (Leustatin) | Injection |
| Dimethyl fumarate (Tecfidera) | Oral |
| Fingolimod (Gilenya) | Oral |
| Glatiramer acetate (Copaxone, Glatopa) | Injection |
| Interferon-β 1a (Avonex, Rebif); peginterferon-β 1a (Plegridy) | Injection |
| Interferon-β 1b (Betaseron, Extavia) | Injection |
| Mitoxantrone (Novantrone) | Infusion |
| Natalizumab (Tysabri) | Infusion |
| Teriflunomide (Aubagio) | Oral |

**33. A**

NMO-IgG antibodies are useful in differentiating patients with acute complete TM due to NMOSD from other etiologies. Patients with NMOSD typically have antibodies to aquaporin-4.

**34. A**

This patient has CIS. Although this MRI result is consistent with ADEM, the patient does not have encephalopathy; therefore, the diagnosis of ADEM cannot be made.

**35. D**

Most children with acute TM have pain, sensory loss, autonomic disturbance, and urinary retention. Infants have a worse prognosis than other children with acute TM.

As in adults, acute TM is more commonly associated with MS if *fewer* than three vertebral segments are involved, and methylprednisolone is the treatment of choice.

**36. True**

The core clinical characteristics of NMOSD are optic neuritis, acute myelitis, area postrema syndrome, acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic syndrome with typical MRI lesions, and symptomatic cerebral syndrome with typical MRI lesions. The area postrema syndrome may manifest with intractable hiccups or vomiting.

A prolonged progressive course is not typical for NMOSD. Infection, sarcoidosis, and cancer can mimic NMOSD. Likewise, acute symptoms are not typical for NMOSD. Abrupt spinal cord symptoms raise concern for ischemia.[3]

**37. A**

Aquaporin-4 is a water channel protein. Patients without antibodies to aquaporin-4 can be diagnosed with NMOSD, but they must meet additional criteria.[3]

**38. A**

Aquaporin-4 is found on the foot processes of astrocytes. NMOSD is an autoimmune astrocytopathy. Binding of antibodies to aquaporin-4 initiates the complement pathway. One of the consequences is breakdown of the blood–brain barrier.[16]

**39. C**

Rituximab, ocrelizumab, and ofatumumab are anti-CD20 monoclonal antibodies and deplete B cells. (CD20 is a B lymphocyte antigen.)

Eculizumab is an antibody to the terminal component of complement (complement protein C5). It is a treatment for NMOSD. Eculizumab is associated with a risk for meningococcal infection. (See Table 7.3 for a list of immunotherapies and their targets.)

*Table 7.3* IMMUNOTHERAPIES

| MEDICATION | ANTIBODY TARGET |
|---|---|
| Alemtuzumab | CD52 |
| Bevacizumab | Vascular endothelial growth factor (VEGF) |
| Daclizumab | CD25 |
| Eculizumab | Complement component C5 |
| Inebilizumab | CD19 |
| Natalizumab | $\alpha_4$ integrin |
| Ocrelizumab | CD20 |
| Ofatumumab | CD20 |
| Rituximab | CD20 |
| Satralizumab | IL-6 receptor |
| Tocilizumab | IL-6 receptor |

**40. B**

Azathioprine is a purine analog. It interferes with purine metabolism and DNA synthesis. Thiopurine methyltransferase is involved in the metabolism of azathioprine. Reduced levels cause accumulation of a toxic metabolite, which can lead to bone marrow suppression.

Aquaporumab blocks other antibodies from binding to aquaporin-4.

Mycophenolate mofetil prevents lymphocyte proliferation. It inhibits inosine-5′-monophosphate dehydrogenase, which is involved in guanosine nucleotide syntheses.[16]

Tocilizumab is an anti-IL-6 receptor antibody. Side effects include opportunistic infections, including tuberculosis.[16]

**41. B**

This patient has ADEM. ADEM is a demyelinating condition caused by inflammation. It is typically monophasic. ADEM is characterized by multifocal neurologic signs, change in consciousness, and typical MRI findings. The brain MRI shows diffuse, bilateral, asymmetric lesions involving the gray and white matter. Lesions are primarily in the cerebral white matter but may also be seen in the thalamus or basal ganglia. Lesions can also be seen in the brainstem, cerebellum, or spinal cord. The lesions are not well demarcated, have increased signal on T2-weighted MRI, and may enhance. ADEM often occurs after a virus infection or vaccination.

Devic disease is now referred to as NMOSD.

**42. A**

ADEM causes perivenular demyelination. Lymphocytes and macrophages surround the veins as well.

**43. D**

Ocrelizumab, which is an antibody to CD20, was the first medication approved by the FDA for primary progressive MS.

**44. B**

Acutely, NMOSD can be treated with corticosteroids and sometimes plasma exchange as well.

Interferon-β, fingolimod, natalizumab, and alemtuzumab can exacerbate NMOSD.

Eculizumab, inebilizumab, and satralizumab are approved therapies for NMOSD.[16]

**45. A**

Hypointense lesions on T1-weighted MRI are rare in ADEM; they are more likely to occur in MS. Periventricular lesions are also less common in ADEM than in MS.

Most children with MS have a relapsing remitting course. Children typically have more relapses than adults early in their disease course. A primary progressive course should raise concern for other diagnoses.[23]

**46. C**

MOG antibodies have been found in some patients with chronic relapsing inflammatory optic neuropathy and in some patients with ADEM who have prominent optic nerve involvement.

Paraneoplastic optic neuropathy is associated with antibodies to CRMP-5. CRMP-5 optic neuritis may be associated with prominent vitreitis and retinal leakage. It also can be associated with TM mimicking NMOSD.[2]

Antibodies to sulfatide or antibodies to GD1a can be seen in certain neuropathies. Antibodies to MAG are discussed below.

**47. A**

An incomplete rim of enhancement is consistent with demyelination. The patient also has punctate hemorrhages on susceptibility-weighted imaging. This occurs in acute hemorrhagic leukoencephalitis. Acute hemorrhagic leukoencephalitis, also known as acute necrotizing hemorrhagic encephalomyelitis, manifests with fever, headache, a stiff neck, and altered mental status. This progresses to focal seizures, weakness, and then coma. It can be fatal. Often, there is a preceding upper respiratory tract infection. Pathology shows hemorrhagic demyelinating lesions with necrosis surrounding blood vessels. There is axonal injury and prominent edema.

An incomplete rim of enhancement, giving a C-shape, may also be seen in the MS variants tumefactive MS and malignant MS. Tumefactive MS is characterized by a demyelinating lesion resembling a tumor. Malignant MS, or Marburg disease, is a fulminant, monophasic condition. Demyelination, axon loss, and necrosis occur.

Baló concentric sclerosis is another MS variant. It is characterized by alternating rings of myelinated and demyelinated tissue.

Marchiafava–Bignami disease is demyelination of the corpus callosum associated with alcohol use.

**48. C**

Macrophage activation syndrome causes an ADEM-like illness that occurs in patients with rheumatic disease (e.g., systemic juvenile idiopathic arthritis). It is characterized by fever, hepatosplenomegaly, lymphadenopathy, increased levels of serum ferritin and triglycerides, and decreased levels of serum fibrin. It can cause purpura and mucosal bleeding. Multiorgan failure can occur. Hemophagocytosis (macrophages engulfing blood cells) is seen in the bone marrow.

POLR3-related leukodystrophy is also known as 4H syndrome. Characteristic features of 4H syndrome are hypomyelination, hypodontia, and hypogonadotropic hypogonadism.[24]

Cerebrotendinous xanthomatosis is a disorder of bile acid synthesis due to a mutation in the gene that encodes sterol 27-hydroxylase (*CYP27A1*). Imaging may show bilateral cerebellar lesions. There may be cortical or cerebellar atrophy. Chenodeoxycholic acid treats the bile acid metabolism defect.[24]

Fabry disease is a lysosomal storage disorder that results from deficiency of α-galactosidase A due to mutations in the *GLA* gene. Patients with Fabry disease can have stroke, white matter abnormalities, and dolichoectasia of cerebral vessels. Patients can also have small-fiber neuropathy, and painful acroparesthesias and angiokeratoma in a bathing suit distribution are characteristic. Patients with Fabry disease are also at risk for

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cardiomyopathy, cardiac conduction defects, autonomic dysfunction, and renal failure. Enzyme replacement therapy is available.

In patients with metachromatic leukodystrophy, the MRI shows bilateral, symmetric signal changes in the periventricular white matter with sparing of the U fibers.

**49. B**

$CD8^+$ T cells are cytotoxic lymphocytes that kill cells infected with virus. $CD8^+$ T cells have been found in patients with neuroimmune reconstitution inflammatory syndrome and Rasmussen encephalitis. HIV-associated $CD8^+$ T cell encephalitis has also been described. In polymyositis, $CD8^+$ T cells infiltrate the muscle.

$CD4^+$ T cells are helper cells. They are depleted in later stages of HIV infection.

Gemistocytes are a type of astrocyte.

Natural killer cells are a type of lymphocyte.

**50. True**

After an injury, remyelination occurs more efficiently in the peripheral nervous system than the CNS.

Oligodendrocytes are the myelin-producing cells in the CNS; Schwann cells are the myelin-producing cells of the peripheral nervous system.

Oligodendrocytes produce many internodes of myelin on multiple axons, so injury to a few oligodendrocytes can produce a noticeable area of demyelination.

Schwann cells produce one internode of myelin and interact with one axon. Schwann cells are close in proximity to the internode of myelin, whereas the oligodendrocyte is connected by long processes (see Table 7.4).

*Table 7.4* COMPARISON OF OLIGODENDROCYTES AND SCHWANN CELLS

| OLIGODENDROCYTES | SCHWANN CELLS |
|---|---|
| **Central nervous system** | **Peripheral nervous system** |
| **Produce many internodes of myelin** | **Produce one internode of myelin; interact with one neuron** |
| **Connected to myelin by long processes** | **In close proximity to myelin** |
| **Remyelination is less efficient.** | **Remyelination is more efficient.** |

**51. A**

PLP is found in the CNS. It is defective in Pelizaeus–Merzbacher disease. Mutations in the gene that encodes PLP (located on the X chromosome) are also associated with hereditary spastic paraparesis.

Myelin basic protein is also found in CNS myelin.

PMP-22 is found in myelin in the peripheral nervous system. Duplication of *PMP22*, which encodes PMP-22, causes Charcot–Marie–Tooth disease type 1A. Deletion of one copy of *PMP22* causes hereditary neuropathy with liability to pressure palsies.

Myelin protein zero is the most prevalent protein in peripheral nervous system myelin. The gene *MPZ* encodes myelin protein zero. Mutations in this gene cause multiple genetic neuropathies. For example, mutations in *MPZ* can cause Charcot–Marie–Tooth disease types 1B, 2I, and 2J; Dejerine–Sottas disease; and congenital hypomyelinating neuropathy.

**52. D**

Most patients with MG have acetylcholine receptor antibodies (anti-AChR antibodies). Acetylcholine receptor antibodies may be measured in binding, blocking, or modulation assays. Many patients with acquired generalized MG or ocular MG have AChR-binding antibodies.

Patients with MG who test negative for acetylcholine receptor antibodies may have muscle-specific receptor tyrosine kinase antibodies (anti-MuSK antibodies). These antibodies are involved in clustering acetylcholine receptors at the neuromuscular junctions. Patients with these antibodies tend to be young females and have less ocular involvement than most patients with MG; their condition may worsen with edrophonium.

**53. A**

MG patients with anti-striated muscle antibodies often have a thymoma. Modulating acetylcholine receptor antibodies are also found in MG patients with thymoma.

**54. B**

PML is caused by reactivation of the JC virus. The pathologic features of PML include intranuclear inclusions in oligodendrocytes; enlarged, bizarre astrocytes; and demyelination.

Extensive perivascular cuffing and necrosis indicates significant inflammation, as might be seen in encephalitis.

**55. B**

Before giving IVIG, it is recommended that the IgA level be checked to rule out IgA deficiency. Patients with IgA deficiency may develop anaphylactic shock if given IVIG, which typically contains IgA.

**56. B**

Morvan syndrome is characterized by limbic encephalitis, neuromyotonia, hyperhidrosis, and polyneuropathy. This is a paraneoplastic condition caused by malignant thymoma. Patients may have potassium channel antibodies.

**57. C**

This patient has epilepsia partialis continua due to Rasmussen encephalitis. It sometimes responds to IVIG. Refractory cases may require hemispherectomy. Some patients with Rasmussen encephalitis have antibodies to the glutamate receptor.

**58. A**

Area postrema syndrome is seen with NMOSD.

Antibodies to MOG injure oligodendrocytes, causing oligodendrocytopathy. The most common MOG-associated disorders (MOGAD) are optic neuritis, ADEM, and myelitis; however, CLIPPERS, focal encephalitis, and progressive leukodystrophy are also MOG-associated disorders.[25]

Optic neuritis in MOGAD is often associated with optic disc edema and peripapillary hemorrhages. It may be bilateral and frequently recurs. There tends to be longitudinally extensive optic nerve involvement with perineural enhancement. Headache may precede visual symptoms. Optic neuritis due to MOGAD is typically steroid responsive.[25] (See Table 7.5 for a comparison of optic neuritis in MS, NMOSD, and MOGAD.)

**59. D**

NMDA receptor encephalitis is due to antibodies against the GluN1 subunit of the NMDA receptor. Symptoms include abnormal behavior or cognition; speech dysfunction; seizures; a movement disorder, dyskinesias, rigidity, or abnormal posture; decreased level of consciousness; and autonomic dysfunction or central hypoventilation. EEG may show focal or diffuse slowing, disorganized activity, epileptiform activity, or extreme delta brushes. The CSF may show pleocytosis or oligoclonal bands. Herpes simplex virus encephalitis and Japanese B encephalitis should be ruled out. An ovarian teratomas is also a known trigger. Treatment is with immunotherapy such as steroids, IVIGs, or plasma exchange. Treatment depends on clinical course rather than antibody levels.[26]

Females with anti-NMDA receptor encephalitis and females with GFAP astrocytopathy are at risk for teratoma.

**60. B**

Monoclonal anti-GM1 antibodies are associated with multifocal motor neuropathy, which is a chronic acquired demyelinating polyneuropathy. Corticosteroids and plasma exchange are *not* helpful in its treatment.

Polyclonal anti-GM1 antibodies are associated with acute motor axonal neuropathies.

Monoclonal anti-MAG antibodies are associated with a demyelinating polyneuropathy.

Polyclonal antibodies to GQ1b are common in Miller–Fisher syndrome, which is characterized by the triad of areflexia, ophthalmoplegia, and ataxia. Polyclonal antibodies to GQ1b are also seen in Bickerstaff brainstem encephalitis. (See Table 7.6.)

**61. C**

Mutations in *SCN9A* can cause primary erythromelalgia (episodes of painful, red extremities), paroxysmal extreme pain disorder, and congenital insensitivity to pain.

Mutations in *EIF2B1* can cause vanishing white matter disease/childhood ataxia with CNS hypomyelination.

Mutations in *GALC* can cause Krabbe disease. In Krabbe disease, galactocerebrosidase activity is decreased and psychosine is elevated.

*Table 7.5* COMPARISON OF OPTIC NEURITIS IN DEMYELINATING CONDITIONS

| DISEASE | MULTIPLE SCLEROSIS | NEUROMYELITIS OPTICA SPECTRUM DISORDER | MYELIN OLIGODENDROCYTE GLYCOPROTEIN-ASSOCIATED DISORDERS |
|---|---|---|---|
| Unilateral or bilateral | Unilateral, but may be bilateral in children | More likely to be bilateral compared to ON in MS | More likely to be bilateral compared to ON in MS |
| Optic disc | Usually not edematous in adults; edema more common in children | May be edematous | Edematous<br>Peripapillary hemorrhages |
| Visual acuity | Central scotoma<br>Vision loss may be more severe in children. | Severe vision loss<br>Altitudinal visual field defect more common than in MS or MOGAD | Severe vision loss |
| MRI | Short lesions of anterior optic nerve | Longitudinally extensive optic nerve lesions involving chiasm | Longitudinally extensive optic nerve lesions<br>Optic nerve sheath/perineural involvement |
| Prognosis | Steroid responsive | Poor response to steroids, may need plasma exchange<br>Less recovery than MS patients | Steroid responsive<br>Frequently recurrent |
| Biomarkers | CSF oligoclonal bands | Antibodies to aquaporin-4<br>CSF eosinophils and neutrophils<br>GFAP | Antibodies to MOG<br>CSF pleocytosis highest[2] |

CSF, cerebrospinal fluid; GFAP, glial fibrillary acidic protein; MOGAD, myelin oligodendrocyte glycoprotein-associated disorder; MS, multiple sclerosis; ON, optic neuritis.

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### *Table 7.6* ANTIBODIES ASSOCIATED WITH ACQUIRED NEUROPATHIES

| DISEASE | TYPE OF ANTIBODIES |
|---|---|
| **Multifocal motor neuropathy** | **Monoclonal anti-GM1 antibodies** |
| **Acute motor axonal neuropathies** | **Polyclonal anti-GM1 antibodies** |
| **Miller–Fisher syndrome** | **Polyclonal antibodies to GQ1b** |
| **Bickerstaff brainstem encephalitis** | **Polyclonal antibodies to GQ1b** |

Mutations in the gene *TREX1*, which encodes 3-prime repair exonuclease 1 (DNAse III), can cause retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (RVCL-S), which can mimic MS. RVCL-S is associated with small-vessel disease, stroke, white matter lesions, migraine-like headaches, and dementia.

Mutations in *TREX1* are also one cause Aicardi–Goutières syndrome. Early onset Aicardi–Goutières syndrome due to *TREX1* mutations can mimic congenital infection. Other genes that cause Aicardi–Goutières syndrome can cause later-onset disease that can mimic ADEM.[24]

Mutations in *TUBB4A* can cause a hypomyelinating leukodystrophy or DYT4 (whispering dysphonia).

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# 8.

# EPILEPSY

## QUESTIONS

1. **A 24-year-old woman presents with an unprovoked seizure. Her family asks about testing and prognosis. Which of the following statements is *false*?**
    - A. An electroencephalogram (EEG) is recommended after the first unprovoked seizure.
    - B. Neuroimaging is recommended after the first unprovoked seizure.
    - C. An echocardiogram and lumbar puncture are recommended.
    - D. The risk for seizure recurrence is the highest during the first 2 years after a seizure.

2. **A 4-year-old girl presents with her first nonfebrile seizure. Which of the following statements is *false*?**
    - A. An EEG is recommended.
    - B. Starting an anti-seizure medication (ASM) will impact her long-term prognosis.
    - C. If the risks of medication are less than the risks associated with a second seizure, an ASM may be prescribed after the first seizure.
    - D. If imaging is performed, magnetic resonance imaging (MRI) is preferred to computed tomography (CT).

3. **A 19-year-old man presents with intractable generalized tonic–clonic (GTC) seizures. His seizures worsen with sleep deprivation. He reports morning twitching and jerks while taking carbamazepine. He said he had similar muscle twitching during his EEG when the light was flashing.**
    - a. What are the expected EEG findings?
        - A. Generalized 4- to 6-Hertz (Hz) polyspike-and-wave discharges with a photoconvulsive response
        - B. Generalized 3-Hz spike-and-wave discharges
        - C. Generalized 2-Hz spike-and-wave discharges
        - D. Left temporal focal epileptiform discharges
    - b. What is the best next step in treatment?
        - A. Add phenytoin.
        - B. Change carbamazepine to oxcarbazepine.
        - C. Change from carbamazepine to levetiracetam.
        - D. Continue carbamazepine and add levetiracetam.

4. **A 6-year-old patient presents with nocturnal GTC seizures. A few seizures have been preceded by facial twitching, drooling, and speech arrest. What are the expected EEG findings?**
    - A. Focal epileptiform discharges over the centrotemporal regions that increase during sleep
    - B. Focal epileptiform discharges over the right frontopolar region
    - C. Focal epileptiform discharges over the midline (at the Cz electrode)
    - D. Generalized epileptiform discharges at 3 to 4 Hz

5. **A 5-year-old patient presents with prolonged nocturnal seizures characterized by eye deviation to the right and unresponsiveness. Seizures are preceded by nausea and accompanied by headache and vomiting. Which of the following is the most likely diagnosis?**
    - A. Self-limited epilepsy with centrotemporal spikes (SeLECTS)
    - B. Childhood occipital visual epilepsy (COVE)
    - C. Juvenile myoclonic epilepsy (JME)
    - D. Self-limited epilepsy with autonomic seizures (formerly Panayiotopoulos syndrome)

6. **An 11-year-old boy has recurrent seizures during the night characterized by hyperkinetic motor activity. Each seizure is brief and is not followed by a postictal period. His mother has a history of similar nocturnal seizures. A defect in which of the following structures is most likely?**
    - A. Sodium channel
    - B. Calcium channel
    - C. Chloride channel
    - D. Nicotinic acetylcholine receptor

7. **A family brings in their 1-week-old child for evaluation. The patient is having multiple brief focal clonic seizures per day. They started at 3 days of life. She has not had fever. The examination findings are normal. Her interictal EEG is normal. The family reports that the patient's father, paternal uncle, and paternal grandmother had similar events, but their seizures resolved before 1 month of age and they had no further neurologic problems. A defect in which of the following structures is most likely?**
    - A. Potassium channel
    - B. Sodium channel
    - C. Calcium channel
    - D. Chloride channel
    - E. Nicotinic acetylcholine receptor

8. **An 8-month-old girl has a GTC seizure associated with a temperature of 101°F. She has another GTC seizure 1 month later, in conjunction with an ear infection with fever. The EEG is normal. The patient's mother states that she herself had seizures with fever from 6 months to 7 years of age. Her sister did as well.**

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**They are both neurologically normal. What diagnosis should be considered?**

A. Febrile seizures plus/genetic epilepsy with febrile seizures plus

B. Self-limited familial neonatal epilepsy (previously benign familial neonatal seizures)

C. Myoclonic epilepsy in infancy

D. Early infantile developmental and epileptic encephalopathy (EIDEE)

E. Self-limited familial infantile epilepsy

**9. A 2-year-old boy presents with daily seizures. He started having seizures at 8 months of age. He has had status epilepticus on three occasions. Two of those episodes occurred with fever. In one episode, the seizure activity was primarily left-sided; the other two times, it was primarily right-sided. He also has a history of myoclonic jerks and head drops. Interictal EEG shows mild diffuse background slowing, a photoparoxysmal response, and generalized 3-Hz spike-and-wave discharges. What is the most likely diagnosis?**

A. Dravet syndrome

B. Lennox–Gastaut syndrome

C. Early-infantile developmental and epileptic encephalopathy (EIDEE)

D. Hemiconvulsion–hemiplegia–epilepsy

E. Myoclonic epilepsy in infancy

**10. A 30-year-old man who has been seizing (left arm clonic activity) for the past 30 minutes arrives in the emergency department. He is given lorazepam and fosphenytoin, and the clonic activity stops. A CT scan of the head was normal, but the patient is difficult to arouse, and his eyes intermittently deviate to the left. What test should be considered?**

A. Positron emission tomography scan

B. Single-photon emission computed tomography

C. EEG

D. Magnetoencephalography

**11. A 26-year-old man has right temporal lobe epilepsy. His seizures have not responded to levetiracetam or cenobamate. What is the best next step?**

A. Referral to an epilepsy monitoring unit for an epilepsy surgery evaluation.

B. Gradually replace cenobamate with lacosamide.

C. Add valproic acid, which has additional mechanisms of action.

D. Referral to neurosurgery for implantation of a vagus nerve stimulator.

**12. A 46-year-old postmenopausal woman with frequent migraines presents after having three focal-onset seizures. Her family history is remarkable for osteoporosis. Her EEG shows occasional right frontal epileptiform discharges. Of the following options, what do you recommend?**

A. Monitor her clinically.

B. Start topiramate.

C. Start vigabatrin.

D. Start carbamazepine.

E. Start phenytoin.

**13. A 9-year-old female patient who is taking valproic acid asks for a different medicine because she is gaining too much weight. The decision is made to transition her from valproic acid to lamotrigine. Three weeks later, the family calls to report a rash that seems to be spreading. What is the next step?**

A. Stop lamotrigine.

B. Send her to her primary care physician for a workup.

C. Check her levels of valproic acid and lamotrigine.

D. Discontinue valproic acid.

**14. A 16-year-old boy with JME presents to the emergency department with increased seizures despite documented good serum levels of lamotrigine. The on-call physician suggests a schedule for starting valproic acid. Later in the week, the patient's mother calls to say that he is sleepy and his gait is unsteady. What should be done first?**

A. Head CT

B. MRI with epilepsy protocol

C. Stat EEG

D. Toxicology screen

E. Verify that his lamotrigine dose was reduced when valproic acid was started

**15. A 24-year-old woman with epilepsy is considering having children. Which of the following statements is *false*?**

A. Pregnancy is associated with a significantly increased risk for status epilepticus, even in women who have been seizure-free.

B. To reduce major congenital malformations and other poor outcomes, valproic acid and polytherapy should be avoided if possible.

C. Children born to mothers who are taking certain ASMs have an increased risk of being small for gestational age.

D. ASMs such as phenobarbital and topiramate are associated with an increased risk of facial clefts.

**16. A 7-year-old boy presents with frequent staring episodes. The mother says he pauses during activities, stares off, and then returns to the activity. She cannot get his attention during the episodes. He is normal afterward. This occurs multiple times per day. His mother states that he once had an episode while blowing a pinwheel. He is otherwise normal, and his neurologic examination is normal. What is the medication of choice?**

A. Ethosuximide

B. Valproic acid

C. Lamotrigine

D. Lacosamide

E. Levetiracetam

**17. A 16-year-old woman with Lennox–Gastaut syndrome has daily myoclonic, atonic, and tonic seizures. Her seizures have not responded to levetiracetam, topiramate, zonisamide, clobazam, cannabidiol, fenfluramine, valproic acid, or rufinamide. If it is**

**decided to pursue another ASM, which of the following medications should be considered?**

A. Felbamate
B. Phenytoin
C. Carbamazepine
D. Gabapentin

**18. Elementary auditory seizures, such as a humming or buzzing sound, arise from which area?**

A. Frontal lobe
B. Mesial temporal lobe
C. Lateral temporal lobe
D. Parietal lobe

**19. Unformed visual hallucinations, such as spots and flashing lights, arise from which area?**

A. Parietal lobe
B. Mesial temporal lobe
C. Lateral temporal lobe
D. Temporal–occipital association cortex
E. Occipital lobe

**20. Formed visual scenes arise from which area?**

A. Parietal lobe
B. Mesial temporal lobe
C. Lateral temporal lobe
D. Temporal–occipital association cortex
E. Occipital lobe

**21. Which of the following statements is *false*?**

A. Patients with juvenile absence epilepsy (JAE) tend to have fewer absence seizures than patients with childhood absence epilepsy (CAE).
B. Absence seizures in JAE tend to be shorter than absence seizures in CAE.
C. Patients with JAE are more likely to have myoclonic and GTC seizures than patients with CAE.
D. Patients with JAE may need lifelong treatment.

**22. Which of the following is most closely associated with faciobrachial dystonic seizures?**

A. Glutamic acid decarboxylase 65 (GAD 65) autoantibodies
B. Immunoglobulin-like cell adhesion molecule 5 (IgLON5) autoantibodies
C. Leucine-rich glioma inactivated protein 1 (LGI1) autoantibodies
D. *N*-Methyl-ᴅ-aspartate (NMDA) receptor autoantibodies

**23. Which of the following is *not* a channelopathy?**

A. Absence epilepsy and episodic ataxia
B. Self-limited familial neonatal epilepsy
C. Generalized epilepsy with febrile seizures plus
D. Autosomal dominant focal epilepsy with auditory features

**24. Autosomal dominant focal epilepsy with auditory features is associated with mutations in which gene?**

A. Nicotinic acetylcholine receptor
B. $\gamma$-Aminobutyric acid A (GABA$_A$) receptor
C. GABA$_B$ receptor
D. Glycine receptor
E. LGI1 gene

**25. Which of the following medications can exhibit zero-order kinetics?**

A. Levetiracetam
B. Valproic acid
C. Phenobarbital
D. Phenytoin

**26. Which of the following medications may be associated with polycystic ovary syndrome and fatal hemorrhagic pancreatitis?**

A. Levetiracetam
B. Valproic acid
C. Phenobarbital
D. Phenytoin
E. Oxcarbazepine

**27. A 30-year-old woman presents in generalized status epilepticus. Which of the following medications should be administered intravenously first?**

A. Fosphenytoin
B. Lacosamide
C. Levetiracetam
D. Lorazepam
E. Valproic acid

**28. A 2-week-old child presents with tonic seizures. The EEG shows burst suppression during wakefulness and sleep. MRI shows hemimegalencephaly. What is the most likely diagnosis?**

A. Epilepsy with myoclonic atonic seizures (formerly known as Doose syndrome)
B. EIDEE
C. Epilepsy in infancy with migrating focal seizures
D. Lennox–Gastaut syndrome
E. West syndrome

**29. Most focal seizures in adults arise from which area?**

A. Frontal lobe
B. Temporal lobe
C. Parietal lobe
D. Occipital lobe

**30. Which of the following is *not* a common feature of seizures arising from the supplemental motor area?**

A. Prolonged duration
B. Tendency to occur during sleep
C. Often stereotypical
D. Multiple occurrences in a single night

**31. Which of the following medications is *least* likely to lower the seizure threshold?**

A. Bupropion
B. Clonidine
C. Tramadol
D. Diphenhydramine
E. Cetirizine

**32. Which of the following ASMs is *not* a T-type (low-voltage–activated) calcium channel blocker?**

A. Ethosuximide
B. Topiramate

C. Valproic acid
D. Zonisamide

**33. Which of the following ASMs is *not* usually associated with weight loss?**
A. Felbamate
B. Levetiracetam
C. Topiramate
D. Zonisamide

**34. Which of the following ASMs is broad spectrum?**
A. Carbamazepine
B. Ethosuximide
C. Oxcarbazepine
D. Valproic acid

**35. Which of the following is the most effective medication for a child with CAE and GTC seizures?**
A. Ethosuximide
B. Oxcarbazepine
C. Lacosamide
D. Valproic acid
E. Vigabatrin

**36. Which of the following medications has high protein binding?**
A. Ethosuximide
B. Gabapentin
C. Levetiracetam
D. Phenytoin
E. Vigabatrin

**37. A 75-year-old woman presents with confusion. Her laboratory studies show hyponatremia. Which of the following medications is most likely to cause this condition?**
A. Oxcarbazepine
B. Lacosamide
C. Clobazam
D. Zonisamide

**38. Which of the following ASMs blocks the metabolism of GABA by GABA transaminase?**
A. Cenobamate
B. Clobazam
C. Ganaxolone
D. Tiagabine
E. Vigabatrin

**39. Which of the following ASMs is *least* likely to affect the eye?**
A. Oxcarbazepine
B. Topiramate
C. Vigabatrin
D. Fenfluramine
E. Clonazepam

**40. Which of the following medications is most likely to increase absence and myoclonic seizures?**
A. Oxcarbazepine
B. Clonazepam
C. Lamotrigine
D. Valproic acid

**41. Fill in the blank: Patients taking ________________ require lower doses of lamotrigine.**
A. Carbamazepine
B. Phenobarbital
C. Phenytoin
D. Valproic acid

**42. Which of the following medications is *least* likely to cause weight gain?**
A. Pregabalin
B. Gabapentin
C. Valproic acid
D. Lamotrigine

**43. Which of the following medications places people of Asian descent with the *HLA-B*1502* antigen at higher risk for Stephens–Johnson syndrome than other patients taking the same medication?**
A. Carbamazepine
B. Lacosamide
C. Valproic acid
D. Topiramate

**44. Patients with short QT syndrome are advised not to take which of the following medications?**
A. Carbamazepine
B. Zonisamide
C. Rufinamide
D. Lacosamide
E. Topiramate

**45. Which of the following medications affects sodium channels differently than the others?**
A. Phenytoin
B. Lamotrigine
C. Oxcarbazepine
D. Lacosamide

**46. Which of the following medications acts on the $\alpha_2\delta$ subunit of high-voltage–activated calcium channels?**
A. Fenfluramine
B. Valproic acid
C. Rufinamide
D. Gabapentin

**47. Which of the following medications modulates synaptic vesicle protein 2A (SV2A)?**
A. Anakinra
B. Lamotrigine
C. Levetiracetam
D. Perampanel
E. Valproic acid

**48. A 5-year-old patient presents with decreased speech and increased seizures. His parents report that he first started having problems with comprehension, then started speaking less. Which of the following EEG findings is most likely?**
A. Frequent left centrotemporal discharges with a horizontal dipole

B. Spike-and-wave activation in sleep with nearly continuous generalized spike-and-wave discharges in non–rapid eye movement sleep
C. Left temporal focal epileptiform discharges
D. Left parietal focal epileptiform discharges

**49. True or false?**
Although it is usually not a first-line treatment, the ketogenic diet is an option for all patients with epilepsy.

**50. Which of the following features is more consistent with psychogenic non-epileptic seizures than with epilepsy?**
A. Tongue-biting
B. The event is stereotyped.
C. Prolonged events that occur only in public settings
D. Significant postictal confusion

**51. Which of the following is most likely to be associated with early onset absence epilepsy?**
A. *CDKL5* mutation
B. *DEPDC5* mutation
C. *GRIN2A* mutation
D. *NHLRC1* mutation
E. *SLC2A1* mutation

**52. For which of the following medications is withdrawal most likely to occur if stopped abruptly?**
A. Perampanel
B. Cenobamate
C. Clobazam
D. Ethosuximide

**53. Which of the following are *least* likely to interact?**
A. Cannabidiol and clobazam
B. Cenobamate and clobazam
C. Fenfluramine and stiripentol
D. Gabapentin and lamotrigine
E. Phenytoin and valproic acid

**54. Which of the following has a box warning for possible suicidal and homicidal ideation?**
A. Brivaracetam
B. Fenfluramine
C. Levetiracetam
D. Perampanel

**55. Which of the following has the highest risk of contributing to serotonin syndrome?**
A. Brivaracetam
B. Cannabidiol
C. Cenobamate
D. Fenfluramine
E. Perampanel

**56. A 40-year-old male with epilepsy is referred to the epilepsy monitoring unit for surgical evaluation. Which of the following is *false*?**
A. Resection of the dominant hippocampus can cause worsening verbal memory.
B. Large temporal lobe resections can cause a homonymous inferior quadrantanopia.
C. Positron emission tomography can help identify epileptogenic regions.
D. Magnetoencephalography can help identify epileptic dipoles and provide functional mapping.
E. Single-photon emission computed tomography can help identify epileptogenic regions.

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# EPILEPSY

## ANSWERS

### 1. C

An EEG and neuroimaging are recommended after a first unprovoked seizure. An electrocardiogram may be helpful if syncope is in the differential. An echocardiogram and lumbar puncture are not routinely indicated in the workup of the first unprovoked seizure.[1] These may be performed if there are other signs/symptoms.

Prolactin can help differentiate GTC seizures from psychogenic nonepileptic seizures if measured within 10–20 minutes after an event.[2]

It is recommended that the patient be informed that the risk for seizure recurrence is the highest during the first 2 years after a seizure. The patient should also be informed that prior brain injury or an EEG showing epileptiform activity increases the risk of recurrence. There is evidence that other MRI abnormalities increase the risk of recurrence. In addition, if the first seizure was nocturnal, there is increased risk of recurrence.[3]

### 2. B

An EEG is recommended. This may help determine recurrence risk and seizure type. It may aid in the diagnosis of an epilepsy syndrome. If neuroimaging is performed, an MRI is preferred; however, a CT may be performed in more urgent situations, such as a prolonged Todd's paralysis or altered mental status.[4]

Anti-seizure medications (ASMs) should not be prescribed to prevent epilepsy in children (or adults). Starting an ASM will *not* impact the patient's long-term prognosis.[3,5]

American Academy of Neurology guidelines recommend that adults presenting with an unprovoked first seizure be advised that an ASM may decrease the risk for seizure recurrence in the first 2 years after a seizure; however, an ASM can cause adverse events and will not change long-term outcome.[3]

### 3a. A and 3b. C

This patient most likely has JME, which is the most common genetic generalized epilepsy syndrome in adults. He is having myoclonic seizures in response to photic stimulation. The EEG will most likely show generalized 4- to 6-Hz polyspike-and-wave discharges with a photoconvulsive response.

Generalized 3-Hz spike-and-wave discharges occur in childhood absence epilepsy (CAE). Generalized 2-Hz spike-and-wave discharges occur in Lennox–Gastaut syndrome.

Carbamazepine and phenytoin can exacerbate myoclonic seizures. Levetiracetam would be a better treatment option. Lamotrigine, topiramate, clobazam, valproic acid, perampanel, zonisamide, and brivaracetam are also options; however, lamotrigine can sometimes increase myoclonic seizures.

### 4. A

The description of this patient's seizures is consistent with self-limited epilepsy with centrotemporal spikes (SeLECTS). (This condition was previously referred to as benign rolandic epilepsy or benign epilepsy with centrotemporal spikes.) The EEG would be expected to show centrotemporal discharges, with a horizontal dipole, that increase in sleep (see Figure 8.1).

Patients with fragile X syndrome can have an EEG resembling the EEG of patients with SeLECTS.[6]

### 5. D

This patient has self-limited epilepsy with autonomic seizures, which was referred to as early onset benign childhood occipital epilepsy (Panayiotopoulos type) in the past. However, the symptoms and interictal discharges are not necessarily occipital in origin. The peak age of onset is 4 or 5 years. Autonomic features, such as nausea and vomiting, are prominent in this syndrome. Seizures are often prolonged and are associated with tonic eye deviation.

Childhood occipital visual epilepsy (COVE syndrome), previously known as late-onset benign occipital epilepsy (Gastaut type), has a mean age at onset of 8 years. It is characterized by elementary visual hallucinations. A migraine-like headache may follow the seizure. Whereas seizures tend to be nocturnal and may be prolonged in self-limited epilepsy with autonomic seizures, seizures are usually brief and diurnal in COVE syndrome. Temporary blindness may occur in COVE syndrome. Interictal occipital discharges may increase significantly when the eyes are not fixated.[7]

### 6. D

This patient most likely has autosomal dominant sleep-related hypermotor epilepsy (ADSHE), formerly known as autosomal dominant frontal lobe epilepsy, which is caused by defects in the genes that encode the nicotinic acetylcholine receptor on chromosomes 15q and 20q. Other causes of ADSHE include mutations in *KCNT1*, *DEPDC5*, and *NPRL3*.[8,9]

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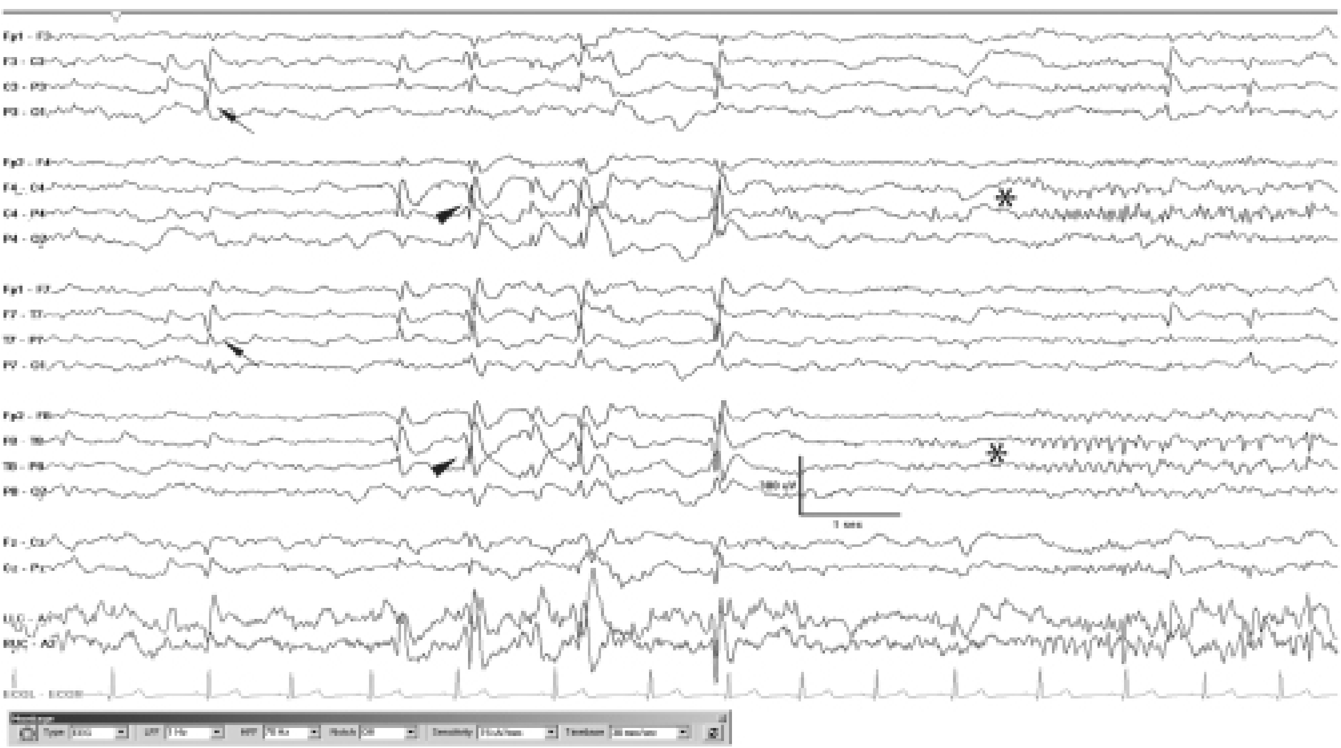

**Figure 8.1** Typical focal epileptiform discharges seen in self-limited epilepsy with centrotemporal spikes (SeLECTS) (formerly benign rolandic epilepsy) (*arrows and arrowheads*), followed by a seizure (*asterisks*) arising from the right centrotemporal region. SOURCE: From Brazil CW, Chong J, Friedman G. *Epilepsy*, Fig. 2-1. New York: Oxford University Press; 2011.

**7. A**

This patient most likely has self-limited familial neonatal epilepsy (formerly benign neonatal familial convulsions), which is most often associated with defects in the potassium channel resulting from mutations in *KCNQ2* on chromosome 20q and *KCNQ3* on chromosome 8q. *KCNQ2* mutations are the most common cause. *KCNQ2* can also cause developmental and epileptic encephalopathy.[10]

**8. A**

This family has febrile seizures plus. It can occur with mutations in *SCN1B* on chromosome 19q or *SCN1A* on chromosome 2q, resulting in sodium channel defects, or with defects in the GABA receptor. There are other less common genetic causes as well.[10]

Self-limited familial neonatal epilepsy (previously benign familial neonatal seizures) typically begins before 1 month of age, often in the first week of life. Seizures often have a focal tonic component at the onset.

Self-limited familial infantile epilepsy is associated with focal seizures that begin between 1 day of life and age 23 months.[10] Some patients with self-limited familial infantile epilepsy have a mutation in the *PRRT2* gene. Patients with mutations in this gene may later develop paroxysmal kinesigenic dyskinesia.[10]

There is also a condition called self-limited familial neonatal–infantile epilepsy. In this condition, family members may have onset of seizures in the neonatal or infantile period. Some of these families have mutations in *SCN2A*. Mutations in *KCNQ2* are less frequent.[10] As mentioned above, mutations in *KCNQ2* can also cause self-limited familial neonatal epilepsy and developmental and epileptic encephalopathy.

Myoclonic jerks would be expected if the patient had myoclonic epilepsy in infancy (formerly benign myoclonic epilepsy).

EIDEE is discussed below.

**9. A**

The patient most likely has Dravet syndrome, which has also been called severe myoclonic epilepsy of infancy. The age at onset, multiple seizure types, photoparoxysmal response, and episodes of status epilepticus with fever support the diagnosis of Dravet syndrome, which is associated with *SCN1A* gene mutations on chromosome 2q. *SCN1A* gene mutations are also found in other types of epilepsy, such as febrile seizures plus.

Sodium channel blockers, including oxcarbazepine, carbamazepine, eslicarbazepine, lacosamide, lamotrigine, phenytoin, and rufinamide, should usually be avoided as maintenance ASMs in patients with Dravet syndrome. Preferred treatments for patients with Dravet syndrome include valproic acid, clobazam, stiripentol, cannabidiol, and fenfluramine. Gene therapy studies for Dravet syndrome are underway.

Lennox–Gastaut syndrome is also associated with multiple seizure types. Tonic, atonic, and atypical absence seizures are common, but any seizure type can occur in this syndrome. The EEG usually shows generalized slow spike-and-wave discharges at 1.5–2.5 Hz and generalized paroxysmal fast activity.

EIDEE is discussed below.

Hemiconvulsion–hemiplegia–epilepsy is an epilepsy beginning in childhood, often in the setting of febrile illness, that is characterized by focal clonic status associated with hemispheric edema, followed by hemispheric atrophy, hemiparesis, and ongoing focal seizures.[6]

Hemiclonic seizures are one of the exclusionary criteria for myoclonic epilepsy in infancy.[10]

**10. C**

Given the patient's prolonged seizure and intermittent eye deviation, an EEG is recommended to confirm the suspected diagnosis of nonconvulsive status epilepticus.

**11. A**

If first-line ASMs fail, the patient should be evaluated in an epilepsy monitoring unit. If the patient is a candidate for temporal lobe epilepsy surgery, it should be offered.[11]

**12. B**

This patient has had three seizures and has an abnormal EEG, so she is at risk for seizures in the future; therefore, treatment should be initiated. Topiramate can be used to prevent migraines and seizures and would be the best option of those listed in the question.

Topiramate has a risk for fetal toxicity; it can cause cleft lip/palate. Offspring born to patients taking topiramate can also be small for gestational age. These risks should be discussed prior to prescribing it to patients with childbearing potential, and folate should be prescribed with topiramate in these patients.[12]

Cytochrome P450 inducers, such as carbamazepine and phenytoin, are associated with increased risk for osteoporosis compared to noninducers. Vigabatrin carries a risk of permanent visual field defects and should not be used for initial treatment in this situation. However, vigabatrin is a preferred treatment for patients with epileptic spasms due to tuberous sclerosis complex.

**13. A**

Due to the risk of life-threatening rash with lamotrigine, it should be discontinued when a rash occurs unless it is absolutely clear that the rash is not drug-related. This patient may see her primary care physician as well, but first lamotrigine should be stopped. It is helpful to have pictures of the rash if possible.

**14. E**

Valproic acid raises the level of lamotrigine by inhibiting its metabolism. This is the reason that lamotrigine is introduced with a different (lower) dose schedule if a patient is already taking valproic acid. It also means that the lamotrigine dose should be decreased when valproic acid is added.

**15. A**

Patients with epilepsy who have been seizure-free for at least 9 months have a good chance of remaining seizure-free during pregnancy.[13] However, levels of ASMs may change during pregnancy, and dose increases may need to be made to prevent seizures. Also, doses of these medications often require adjustment in the postpartum period.[14]

It is recommended that patients with childbearing potential taking ASMs take folate to prevent neural tube defects and minimize the risk for poor neurodevelopmental outcomes.[12]

Consideration of avoidance of the use of valproic acid is also recommended because of the numerous birth defects with which it is associated, including neural tube defects and urogenital and renal malformations. Offspring may also be small for gestational age. In addition, use of valproic acid during pregnancy is associated with a decrease in the child's intelligence quotient and a risk for autism spectrum disorder.[12]

Phenobarbital is associated with a risk for cardiac malformations and oral clefts.[12]

Medications such as oxcarbazepine, lamotrigine, and levetiracetam are associated with lower risks for major congenital malformations.[12]

**16. A**

Ethosuximide is the medication of choice for initial treatment of CAE in patients without GTC seizures. A double-blind, randomized, controlled trial was performed comparing ethosuximide, lamotrigine, and valproic acid in the treatment of CAE. Ethosuximide and valproic acid were more effective than lamotrigine. Valproic acid had more side effects than ethosuximide. Therefore, ethosuximide is the best choice if the patient does not have GTC seizures.[15]

**17. A**

Felbamate is the most likely of these medications to help this patient. The ketogenic diet and a neurostimulation device are also options. If she is falling and injuring herself with her seizures, corpus callosotomy may be helpful.

**18. C**

Elementary auditory seizures, such as a humming or buzzing sound, arise from the lateral temporal lobe.

**19. E**

Unformed visual hallucinations arise from the occipital lobe.

**20. D**

Formed visual scenes arise from temporal–occipital association cortex.

**21. B**

Patients with JAE tend to have fewer seizures than patients with CAE, but the seizures are longer. Patients

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with JAE are also more likely to have myoclonic and GTC seizures than patients with CAE.

**22. C**

Anti-leucine-rich glioma inactivated protein 1 (LGI1) encephalitis often presents with seizures. Faciobrachial dystonic seizures are a characteristic seizure type seen in these patients. They may also have hyponatremia.

GAD autoantibodies can cause stiff person syndrome but also can cause seizures, including musicogenic seizures.

Patients with immunoglobulin-like cell adhesion molecule 5 (IgLON5) autoantibodies can have symptoms that mimic Huntington disease as well as bulbar, gait, and sleep abnormalities.

Seizures and an extreme delta brush EEG pattern can be seen in patients with anti-NMDA receptor encephalitis, which can be associated with ovarian teratoma.

**23. D**

Autosomal dominant focal epilepsy with auditory features, previously known as familial autosomal dominant lateral temporal lobe epilepsy, is not a channelopathy.

Absence epilepsy and episodic ataxia is caused by mutations in the gene *CACNA1A*, which encodes the principal subunit of the P/Q calcium channel.

Febrile seizures plus/generalized epilepsy with febrile seizures plus can result from sodium channel mutations. Mutations in the $\text{GABA}_A$ receptor have also been associated with febrile seizures plus (see Table 8.1).

*Table 8.1* CHANNELOPATHIES THAT CAUSE EPILEPSY

| EPILEPSY SYNDROME | CHANNEL AFFECTED |
|---|---|
| **Absence epilepsy and episodic ataxia** | **Calcium** |
| **Self-limited familial neonatal epilepsy** | **Potassium** |
| **Febrile seizures plus (generalized epilepsy with febrile seizures plus syndrome)** | **Sodium most commonly but also $\text{GABA}_A$ receptor** |

GABA, γ-aminobutyric acid.

**24. E**

Autosomal dominant focal epilepsy with auditory features is associated with mutations in the LGI1 gene.

**25. D**

Phenytoin exhibits first-order kinetics to a certain point, and then it exhibits zero-order kinetics. Initially, a certain percentage of the drug is eliminated in a specific time period (first-order kinetics). Then, when its metabolic pathways are saturated, metabolism of phenytoin changes to zero-order kinetics (i.e., a specific amount is metabolized in a specific time period). When this occurs, a small increase in dose will cause a large increase in the blood level.

Carbamazepine also has nonlinear metabolism. It induces its own metabolism.

**26. B**

Valproic acid is associated with polycystic ovary syndrome and fatal hemorrhagic pancreatitis.

**27. D**

A benzodiazepine is the first-line treatment for generalized status epilepticus in children and adults.[16]

**28. B**

This patient has early-infantile developmental and epileptic encephalopathy (EIDEE), which is a typically difficult to control epilepsy that presents in the first 3 months of life. (Patients who previously would have been diagnosed with Ohtahara syndrome or early myoclonic encephalopathy are now diagnosed with EIDEE.) The neurological exam is often abnormal, and patients with EIDEE have developmental delay. The interictal EEG is abnormal, demonstrating background slowing and burst suppression or multifocal epileptiform discharges. Multiple seizure types are associated with EIDEE. These patients may have tonic seizures, myoclonic seizures, epileptic spasms, or sequential seizures (which may include tonic seizures, clonic seizures, seizures with autonomic features, or seizures with automatisms). EIDEE has multiple etiologies, including structural, metabolic, and genetic causes (e.g., mutations in *KCNQ2*, *SCN2A*, *SCN8A*, *STXBP1*, *CDKL5*, or *KCNT1*). Sometimes seizure types/semiology aid in prediction of the genetic condition.[10]

West syndrome refers to the triad of epileptic spasms, developmental stagnation/regression, and hypsarrhythmia. In the 2022 International League Against Epilepsy classification and definition of epilepsy syndromes with onset in neonates and infants article, West syndrome is included in the category of infantile epileptic spasms syndrome.[10]

Epilepsy with myoclonic atonic seizures (EMAtS; formerly Doose syndrome) presents in late infancy or early childhood. Tonic seizures do not usually occur in EMAtS. (A patient with myoclonic, astatic, and tonic seizures is more likely to have Lennox–Gastaut syndrome than EMAtS.) Multiple genes are associated with EMAtS; some patients have GLUT1 deficiency syndrome due to mutations in *SLC2A1*.

Epilepsy in infancy with migrating focal seizures usually is not associated with a burst suppression EEG pattern. It is associated with intractable focal seizures and encephalopathy. It is often due to mutations in *KCNT1*, which encodes a potassium channel. Mutations in *KCNT1* can cause multiple other epilepsy syndromes as well, including KCNT1-related developmental epileptic encephalopathy and autosomal dominant sleep-related hypermotor epilepsy. Some patients with *KCNT1* mutations have been treated with quinidine, but there is a risk for QTc prolongation and arrhythmia.

**29. B**

Most focal seizures in adults arise from the temporal lobe.

**30. A**

Seizures arising from the supplemental motor area tend to be brief, begin and end quickly, and occur out of sleep. They may occur multiple times in a single night. Hypermotor activity with asymmetric tonic posturing is typical. A fencing posture may be seen. The patient may retain consciousness. Patients recover quickly, typically without postictal confusion. Ictal EEG findings are often less prominent than during other seizure types.

**31. E**

Cetirizine (Zyrtec) is *least* likely to lower the seizure threshold (see Box 8.1).

### *Box 8.1* MEDICATIONS THAT LOWER THE SEIZURE THRESHOLD

- Bupropion (Wellbutrin)
- Clonidine
- Clozapine
- Cyclosporin
- Diphenhydramine
- Imipenem
- Lithium
- Meperidine
- Theophylline
- Tacrolimus
- Tramadol

**32. B**

Topiramate is *not* a T-type calcium channel blocker.

Ethosuximide, valproic acid, and zonisamide are T-type calcium channel blockers. T-type calcium channels are involved in the generation of absence seizures. Some patients with CAE have mutations in *CACNA1H*, the gene encoding the calcium channel, voltage-dependent, T-type, $\alpha_{1H}$ subunit.

**33. B**

Levetiracetam usually does not affect weight.

Felbamate, topiramate, and zonisamide can all decrease appetite and cause weight loss.

**34. D**

Valproic acid is a broad-spectrum anti-seizure medication. It can be used to treat focal and generalized seizures.

Ethosuximide is used primarily for absence seizures.

Phenytoin, oxcarbazepine, and carbamazepine are used for focal seizures and can exacerbate certain types of seizures in patients with genetic generalized epilepsy.

**35. D**

If a patient with CAE has GTC seizures, valproic acid is preferred to ethosuximide. Both medications treat absence seizures; however, ethosuximide does not treat GTC seizures. Lamotrigine would be an alternative if valproic acid is contraindicated.

Tiagabine and vigabatrin can *cause* absence status. Medications such as these, which increase $GABA_B$ activity, can increase absence seizures.[17]

**36. D**

Phenytoin has high protein binding (>75%). Low albumin levels result in higher levels of free phenytoin. Ethosuximide, gabapentin, levetiracetam, and vigabatrin have low protein binding (<10%).

**37. A**

Of the options listed, oxcarbazepine is the most likely to cause hyponatremia. Carbamazepine and eslicarbazepine (Aptiom) also can cause hyponatremia.

**38. E**

Vigabatrin inhibits the breakdown of GABA by GABA transaminase.

Ganaxolone is a neurosteroid that acts as a positive allosteric modulator of $GABA_A$ receptors, acting at a site distinct from benzodiazepines and barbiturates. Like barbiturates, ganaxalone acts at synaptic and extrasynaptic $GABA_A$ receptors. It is being studied as a treatment for refractory status epilepticus, during which synaptic $GABA_A$ receptors are internalized.[18] Ganaxolone is approved to treat patients with epilepsy due to CDKL5 deficiency disorder.

Tiagabine blocks glial and presynaptic reuptake of GABA.

Cenobamate and clobazam are discussed below.

**39. A**

Oxcarbazepine is *least* likely to affect the eye.

Topiramate can cause angle-closure glaucoma. Benzodiazepines have also been associated with a risk for angle-closure glaucoma, and the medications nasal diazepam and nasal midazolam both have warnings regarding use in patients with glaucoma. Fenfluramine can increase the risk for glaucoma as well.

Vigabatrin can cause visual field defects. Vigabatrin can also cause hyperintensities on T2-weighted MRI.

**40. A**

Carbamazepine and oxcarbazepine can exacerbate absence and myoclonic seizures.

Lamotrigine can sometimes increase myoclonic seizures, but it is a treatment for absence seizures. It is used in some patients with JME even though there is a risk that myoclonic jerks may worsen.

Valproic acid treats both absence and myoclonic seizures, but it is teratogenic.

Clonazepam can be used for myoclonic seizures, but it is usually not a first-line treatment for absence seizures.

**41. D**

Valproic acid inhibits the metabolism of lamotrigine. Valproic acid reduces glucuronidation, leading to reduced clearance of lamotrigine. Therefore, lamotrigine is increased to a lower total dose in patients on valproic acid.

Carbamazepine, phenobarbital, and phenytoin are all inducers. Therefore, lamotrigine can be increased more quickly than it would be if given alone.

**42. D**

Lamotrigine does not usually cause weight gain or weight loss.

Gabapentin, pregabalin, valproic acid, and carbamazepine can cause weight gain. Gabapentin and pregabalin can also cause peripheral edema.

**43. A**

People of Asian descent with the *HLA-B*1502* antigen who take carbamazepine are at higher risk for Stephens–Johnson syndrome.

**44. C**

Patients with short QT syndrome are advised not to take rufinamide (Banzel) or cenobamate (Xcopri). Both rufinamide and cenobamate can shorten the QT interval.

Lacosamide can prolong the PR interval.

**45. D**

Most ASMs that affect the sodium channel act when it is in its fast-inactivated state. Lacosamide affects the slow-inactivated state of voltage-gated sodium channels.

**46. D**

Both gabapentin and pregabalin act on the $\alpha_2\delta$ subunit of high-voltage–activated calcium channels. The U.S. Food and Drug Administration has issued a warning about possible serious breathing problems in patients taking gabapentin or pregabalin who have respiratory risk factors, such as patients taking opioid pain medications or other central nervous system depressants and patients with decreased lung function.[19]

**47. C**

Levetiracetam modulates SV2A, which is a synaptic vesicle protein. This effect is thought to be related to its mechanism of action. Brivaracetam has a high affinity for SV2A.

Anakinra is an interleukin-1 (IL-1) receptor antagonist. It prevents binding of IL-1α and IL-1β. It has been used in new-onset refractory status epilepticus that does not respond to other treatments.

Perampanel is a noncompetitive α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptor antagonist.

**48. B**

This patient has Landau–Kleffner syndrome, which historically has been associated with electrical status epilepticus in sleep. It also has been called acquired epileptic aphasia. More recently, Landau–Kleffner syndrome has been classified as a subtype of epileptic encephalopathy with spike-and-wave activation in sleep (EE-SWAS), associated with language regression, specifically acquired auditory agnosia.[6] Patients with Landau–Kleffner syndrome develop verbal auditory agnosia, and then expressive language deteriorates. Typically, the patient has seizures, but they are not frequent. Peak age of seizure onset is 4 or 5 years, and worsening of the EEG and cognition occurs 1 or 2 years later. The EEG shows significant worsening in sleep with 1.5–2 Hz spike-and-wave complexes in non–rapid eye movement sleep.[6] Steroids and high-dose diazepam are common treatments, but many other medications have been used. Carbamazepine and phenytoin can exacerbate the EEG findings and should generally be avoided.

Epileptic encephalopathy with spike-and-wave activation in sleep (EE-SWAS) is associated with initially normal development. Developmental epileptic encephalopathy with spike-and-wave activation in sleep (DEE-SWAS) is seen in patients with preexisting neurological conditions.[6] Thalamic injury is a risk factor for these conditions.

**49. False**

The ketogenic diet is a high-fat diet used to treat epilepsy. In a 3:1 ratio ketogenic diet, the patient consumes three times as much fat as protein and carbohydrate combined (i.e., for every 3 g of fat, there is 1 g of combined protein and carbohydrate). The ketogenic diet is often initiated in the hospital because of the risks of vomiting, hypoglycemia, and dehydration. Patients on this diet should not be given dextrose in their intravenous fluids. Possible complications of the diet include kidney stones, constipation, hyperlipidemia, reduced bone mass, and decreased growth.

The ketogenic diet is *not* an option for all patients with epilepsy. The ketogenic diet can be lethal in certain metabolic conditions associated with seizures, such as pyruvate carboxylase deficiency. It is contraindicated in many other metabolic conditions, such as acute intermittent porphyria, cytochrome oxidase deficiency, carnitine deficiency, defects in oxidation of free fatty acids, and certain mitochondrial conditions.

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The ketogenic diet is particularly helpful for patients with glucose transporter type 1 deficiency (Glut1-DS) and pyruvate dehydrogenase (E1) deficiency.

Topiramate and zonisamide should be used cautiously in patients on the ketogenic diet because these drugs can cause metabolic acidosis and kidney stones. Topiramate causes calcium phosphate (rather than calcium oxalate) stones.

Other dietary therapies include low glycemic index treatment, the modified Atkins diet, and the medium-chain triglyceride diet.

**50. C**

Tongue-biting (the side of the tongue), stereotyped events, incontinence, occurrence during sleep, significant postictal confusion, and injuries during events are suggestive of epilepsy. Prolonged events that occur only in public settings raise concern for psychogenic nonepileptic seizures (PNES). However, the gold standard for diagnosing PNES is video-EEG monitoring.

**51. E**

Early onset absence epilepsy can be seen in patients with *SLC2A1* (solute carrier family 2 [facilitated glucose transporter] mutations). In addition, *SLC2A1* mutations can cause Glut1-DS, alternating hemiplegia of childhood, and a paroxysmal exertional dyskinesia with choreoathetosis designated as PxMD-*SLC2A1* (DYT9/DYT18). Glut1-DS may manifest as refractory epilepsy in infants. The preprandial EEG may be worse than the postprandial EEG.

Mutations in *CDKL5*, which encodes cyclin-dependent–like kinase 5, cause an X-linked developmental epileptic encephalopathy. CDKL5 deficiency disorder shares some features of Rett syndrome; however, patients with CDKL5 deficiency disorder tend to lack a period of normal development and have more developmental delays than patients with Rett syndrome. In addition, patients with CDKL5 deficiency disorder have a higher risk for epilepsy, cortical vision impairment, and subtle facial dysmorphic features.

Mutations in *DEPDC5* can cause mammalian target of rapamycin (mTOR) activation. *DEPDC5* mutations can cause certain familial focal epilepsies as well as cortical dysplasia. Mutations in this gene have also been linked to epileptic spasms and sudden unexpected death in epilepsy.[20]

*GRIN2A* mutations have been found in patients with SeLECTS that evolves to EE-SWAS.[6]

Mutations in *NHLRC1*, which is also known as *PME2B*, are one cause of the progressive myoclonic epilepsy Lafora disease. *NHLRC1*/*PME2B* encodes malin.

**52. C**

Clobazam is a benzodiazepine. It increases the frequency of opening of the chloride channel of the $GABA_A$ receptor when GABA binds to the receptor. Abrupt discontinuation can cause withdrawal. Clobazam does carry a risk for Stevens–Johnson syndrome.

**53. D**

Gabapentin and lamotrigine are least likely to interact.

Cannabidiol inhibits CYP3A4 and CYP2C19, which are involved in metabolizing clobazam and *N*-desmethylclobazam, respectively. Increased levels of *N*-desmethylclobazam, an active metabolite of clobazam, can result in sedation if the dose of clobazam is not reduced.[21]

Like cannabidiol, cenobamate can increase *N*-desmethylclobazam levels. Cenobamate also can increase phenytoin and phenobarbital levels, but it can cause reduced lamotrigine, carbamazepine, and oral contraceptive levels. (The mechanism of action of cenobamate is not clear. It inhibits voltage-gated sodium currents and is a positive allosteric modulator of the $GABA_A$ receptor [independent of the benzodiazepine site].)[22]

The recommended dose of fenfluramine is reduced for patients on stiripentol and clobazam.[23] Stiripentol can inhibit many of the enzymes that are involved in metabolizing fenfluramine (e.g., CYP1A2, CYP2B6, CYP3A4, and CYP2C19).

Similar to cannabidiol, stiripentol increases plasma levels of clobazam due to inhibition of CYP3A4 and increases levels of *N*-desmethylclobazam due to inhibition of CYP2C19. Stiripentol can affect appetite and cause neutropenia and thrombocytopenia.[24]

Certain patients, including some patients of Asian background, may have reduced activity of CYP2C19, which is responsible for metabolism of *N*-desmethylclobazam, diazepam, and phenytoin. Testing for this condition is available.

Phenytoin induces hepatic enzymes and can lower levels of valproic acid. Valproic acid inhibits enzymes in the P450 system and can increase levels of phenytoin. Valproic acid also displaces phenytoin from plasma proteins, resulting in increased levels of free phenytoin.

Combining cannabidiol and valproic acid increases the risk for elevation of liver enzymes.

**54. D**

Perampanel has a box warning for serious behavioral and psychiatric side effects, including homicidal and suicidal ideation.[25]

**55. D**

Fenfluramine and its metabolite norfenfluramine are agonists at serotonin 5-$HT_2$ receptors. There is a link between 5-$HT_{2B}$ receptor agonists and valvular heart disease and pulmonary arterial hypertension. Therefore, echocardiograms are routinely performed in patients on fenfluramine. Fenfluramine can also decrease appetite and weight, increase blood pressure, cause somnolence, and increase the risk for glaucoma.[23]

**56. B**

Large temporal lobe resections can cause a homonymous superior quadrantanopia (pie in the sky) defect.

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# 9.

# METABOLIC DISORDERS

## QUESTIONS

1. **Which of the following conditions is *least* likely to cause hyperammonemia?**
   A. Citrullinemia
   B. Isovaleric acidemia
   C. Maple syrup urine disease (MSUD)
   D. Medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency

2. **A neonate has seizures that do not respond to lorazepam, diazepam, fosphenytoin, phenobarbital, or levetiracetam. Which of the following medications should be administered next?**
   A. Topiramate
   B. Zonisamide
   C. Pyridoxine
   D. Valproic acid

3. **Fill in the blank: The conditions __________________ and __________________ have been found to be allelic disorders.**
   A. Biotinidase deficiency and pyridoxine deficiency
   B. Folinic acid–responsive seizures and pyridoxine-dependent epilepsy
   C. Phenylketonuria (PKU) and neopterin reductase deficiency
   D. Sepiapterin reductase deficiency and biopterin deficiency

4. **A previously healthy 1-year-old boy presents with new-onset seizure. He has had vomiting, lethargy, and refusal to eat. He was diagnosed with a viral infection by his pediatrician on the day before admission. The examination is remarkable for hepatomegaly. Laboratory results show hypoketotic hypoglycemia, an elevated ammonia level, and hyperuricemia. What is the most likely diagnosis?**
   A. Classic galactosemia
   B. Lowe syndrome
   C. Medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency
   D. Glycogen storage disease type V (McArdle disease)

5. **A 3-year-old macrocephalic boy presents with lethargy, dystonia, and hypotonia associated with a gastrointestinal illness. Magnetic resonance imaging (MRI) scan shows bilateral widening of the Sylvian fissures and increased T2 signal in the basal ganglia. What is the suspected diagnosis?**
   A. Cerebral folate deficiency
   B. Glutaric aciduria type I
   C. Miller–Dieker syndrome
   D. Mowat–Wilson syndrome

6. **A 5-year-old boy is adopted from another country. His mother would like him to be evaluated for developmental delay. On examination, he is microcephalic. He has pale blond hair, eczema, and a musty odor. MRI shows delayed myelination. What is the most likely diagnosis?**
   A. Biotinidase deficiency
   B. Phenylketonuria (PKU)
   C. Sulfite oxidase deficiency
   D. Thiamine deficiency

7. **A 7-day-old infant presents with seizures, lethargy, opisthotonus, and sweet-smelling urine. Ketonuria is found on laboratory testing. MRI shows diffuse cerebral white matter edema. Which of the following treatments would be most successful?**
   A. Administer carnitine.
   B. Administer riboflavin.
   C. Restrict branched-chain amino acids.
   D. Restrict glucose.

8. **An infant presents with hypotonia, apnea, and intractable myoclonic seizures. He has a history of hiccups, perhaps even in utero. The electroencephalogram (EEG) shows burst suppression. What is the most likely diagnosis?**
   A. Glucose transporter defect
   B. Infantile 3-phospholycerate dehydrogenase deficiency
   C. Molybdenum cofactor deficiency
   D. Nonketotic hyperglycinemia (NKH)

9. **An infant presents with new-onset seizures. He has a history of failure to thrive. He has axial hypotonia, and his reflexes are difficult to obtain. Although he is thin, he has a fat pad above his buttocks. His nipples are inverted. Which of the following tests is most likely to aid in the diagnosis of this patient?**
   A. Cerebrospinal fluid (CSF) neurotransmitters
   B. Lipid panel
   C. Serum amino acids
   D. Transferrin isoform analysis

10. **A 5-day-old newborn develops poor feeding, vomiting, and lethargy. Laboratory studies indicate acidosis, ketosis, hyperammonemia, and neutropenia. Which test is most likely to confirm his diagnosis?**
    A. Chromosomal microarray
    B. Copper level
    C. Lumbar puncture

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D. Urine organic acids by gas chromatography–mass spectrometry

**11. A 3-month-old patient presents with seizures. On examination, he is thin and hypotonic. His hair is light and sparse. Pili torti is seen when the hair is examined under light microscopy. Which of the following is the most likely cause?**

A. A defect in copper-transporting adenosine triphosphatase (ATPase)
B. A defect in inositol polyphosphate 5-phosphatase OCRL-1
C. Mutation in the *PANK2* gene
D. Mutation in the *C19orf12* gene

**12. A woman presents with altered mental status and hyperammonemia after being prescribed valproic acid. She has a history of recurrent vomiting attributed to a migraine variant. The patient and her mother are vegetarians. The patient's brother died in the newborn period of an unknown cause. What is the most likely diagnosis?**

A. Hartnup disease
B. Ornithine transcarbamylase deficiency
C. Tangier disease
D. Wolman disease

**13. Which of the following conditions is *least* likely to occur in mucopolysaccharidoses (MPS)?**

A. Carpal tunnel syndrome
B. Diabetes
C. Hydrocephalus
D. Cord compression

**14. A 4-year-old child presents with loss of milestones. MRI demonstrates bilateral, symmetric, diffuse increased signal in the periventricular white matter. Nerve conduction studies show slowed conduction velocities. Nerve biopsy demonstrates lipid deposits. Which of the following is *not* typical of this condition?**

A. Decreased arylsulfatase A activity
B. Decreased protein in the CSF
C. Delayed nerve conduction velocities
D. Increased urine sulfatide excretion

**15. An 8-year-old boy is brought to the clinic because of worsening school performance. His mother reports that he was diagnosed with attention-deficit/hyperactivity disorder (ADHD) at age 6 years. However, he has had an increase in staring-off episodes despite stimulant medication. His handwriting has deteriorated, and he cannot follow oral instructions. MRI shows symmetric increased T2 signals in the parieto-occipital regions. Which laboratory test is most likely to be abnormal?**

A. Echocardiogram
B. Lipid panel
C. Skeletal survey
D. Very-long-chain fatty acids

**16. Which laboratory study or studies are useful in the diagnosis of peroxisome biogenesis disorders such as Zellweger disease?**

A. Cathepsin D
B. Phytanic acid, pristanic acid, and pipecolic acid
C. Palmitoyl-protein thioesterase 1
D. Tripeptidyl-peptidase 1

**17. A 15-month-old patient presents with seizures and loss of milestones. Examination shows macrocephaly, frontal bossing, hyperreflexia, and spasticity. Brain MRI shows increased T2 signal in the bifrontal white matter. A defect in which of the following genes is most likely?**

A. *GFAP*
B. *PCDH19*
C. *PRICKLE1*
D. *STXBP1*

**18. Which of the following is a neurodegenerative disease, caused by mutations in the proteolipid protein 1 (*PLP1*) gene, which results in nystagmus, stridor, hypomyelination, and initial hypotonia followed by spasticity?**

A. Aicardi–Goutières syndrome
B. Cerebrotendinous xanthomatosis
C. GM1 gangliosidosis
D. Pelizaeus–Merzbacher disease

**19. Which of the following diseases is associated with mutations in the genes encoding subunits of the eukaryotic translation initiation factor 2B (eIF2B), foamy oligodendrocytes, decreased CSF asialotransferrin, and deterioration after stress?**

A. Cerebrotendinous xanthomatosis
B. Childhood ataxia with central nervous system hypomyelination/vanishing white matter disease (CACH/VM)
C. Farber disease
D. 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) lyase deficiency

**20. Which of the following conditions can mimic congenital infection and cause CSF lymphocytosis and calcifications in the basal ganglia?**

A. Aicardi–Goutières syndrome
B. Kearns–Sayre syndrome
C. Hereditary diffuse leukoencephalopathy with spheroids
D. Megalencephalic leukoencephalopathy with subcortical cysts

**21. Which of the following leukodystrophies causes cataracts, dementia, ataxia, and elevated cholestanol?**

A. Adult-onset polyglucosan body disease
B. Cerebrotendinous xanthomatosis
C. HMG-CoA lyase deficiency
D. L2-hydroxyglutaric aciduria

**22. An 8-month-old child presents with regression. The family reports that the patient became irritable at approximately 5 months of age. He stopped**

**progressing developmentally and has been losing milestones recently. He has intermittent fever, but no infection has been found. He is hypertonic and does not visually track. Lumbar puncture shows elevated protein. Which enzyme is most likely to be deficient?**

A. Ceramidase
B. Galactocerebrosidase
C. Neuraminidase
D. Sphingomyelinase

23. **A 6-month-old boy presents with loss of milestones. He can no longer hold up his head or roll over. On examination, he has strabismus, stridor, hepatosplenomegaly, and hyperreflexia. During the examination, he repeatedly retroflexes his neck. Bone marrow analysis shows abnormal cells. What other finding is expected?**

A. Aromatic L-amino acid decarboxylase (AADC) deficiency
B. Glucocerebrosidase deficiency
C. Guanidinoacetate methyltransferase (GAMT) deficiency
D. Creatine transporter (SLC6A8) deficiency

24. **An infant presents with motor regression. She is macrocephalic and hypotonic. Canavan disease is suspected. Which test would aid in this diagnosis?**

A. Uric acid
B. Urine *N*-acetyl aspartate (NAA)
C. Urine oligosaccharides
D. Urine glycosaminoglycans

25. **A 1-year-old child presents with developmental delay. The family reports that she was normal at birth, but then they noticed a significant startle to noises. Due to concerns about her vision, she saw an ophthalmologist who "said something about fruit in her eye." On examination, she is hypotonic and hyperreflexic. There is no hepatosplenomegaly. What other finding(s) might you expect?**

A. Bony defects
B. Deficiency of hexosaminidase A
C. Microcephaly
D. Cardiomyopathy

26. **A 15-year-old boy presents with lancinating extremity pain, which worsens in the summer. On review of systems, he lists abdominal pain. On examination, he has dark red dots near his umbilicus and on his thighs and buttocks. Which of the following conditions is *least* likely to occur in this disease?**

A. Deafness
B. Hypertension
C. Myocardial infarction
D. Stroke

27. **An 11-year-old girl presents with unsteadiness, seizures, and deteriorating school performance. On examination, she is unable to look upward, has dysarthria, and is ataxic. Bone marrow analysis reveals sea-blue histiocytes and foam cells. Filipin staining shows accumulation of cholesterol in lysosomes of cultured fibroblasts. Which other condition is most likely to be associated with this disease?**

A. Cataplexy
B. Conductive hearing loss
C. Growth hormone deficiency
D. Renal calculi

28. **A 3-year-old boy presents with epilepsy and decreased vision. On EEG, occipital spikes are seen at low-frequency stimulation. Visual evoked potentials are high in amplitude. The patient's sister had similar symptoms. She regressed, lost her vision, is ataxic, and has action myoclonus and myoclonic epilepsy. She is scheduled for a biopsy. Which of the following findings is most likely?**

A. Electron-dense granules within the smooth muscle layer of small arterial vessels
B. Curvilinear profiles within lysosomes
C. Spheroids on nerve biopsy
D. Ragged red fibers on muscle biopsy

29. **A cherry-red spot, severe myoclonus, seizures, and night-blindness are found in which of the following diseases?**

A. Lafora disease
B. Marinesco–Sjögren syndrome
C. Sialidosis type I
D. Unverricht–Lundborg disease

30. **A child presents with weakness, myoclonus, and generalized seizures. The mother and maternal grandmother have optic atrophy, hearing loss, and lipomas. Which of the following is most likely to be present?**

A. Aggregates of polyglucosan in the apocrine and eccrine glands on skin biopsy
B. Elevated lactate
C. Potassium channel defect
D. Scoliosis

31. **Mutations in which of the following genes cause glucose transporter type 1 deficiency syndrome (also known as Glut1-DS or Glut-1 deficiency), early onset absence epilepsy, alternating hemiplegia of childhood, paroxysmal choreoathetosis with episodic ataxia and spasticity (DYT9), and epilepsy with exercise-induced dyskinesia (DYT18)?**

A. *CACNA1A*
B. *GABRAG2*
C. *PLA2G6*
D. *SLC2A1*

32. **Which of the following is the best treatment for Glut1-DS?**

A. Carnitine
B. Clonazepam
C. Sulfonylurea
D. The ketogenic diet

33. **A 3-month-old infant presents with respiratory failure during a viral infection. She is hypotonic and**

**developmentally delayed. MRI shows symmetric, increased signal in the basal ganglia. The CSF lactate level is elevated. What is the most likely diagnosis?**

A. Idiopathic basal ganglia calcification-1 (formerly called Fahr disease)
B. Kernicterus
C. Leigh syndrome
D. Neurodegeneration with brain iron accumulation (NBIA)

**34. Fill in the blank: Depakote is contraindicated in patients with __________________.**

A. *CHRNA2* mutations
B. *POLG* mutations
C. *SCN1A* mutations
D. Type II hyperprolinemia

**35. A 5-year-old boy presents with a history of cerebral palsy. He has a history of hypotonia and delayed milestones. Currently, he has hyperreflexia and dystonia. He has scars from biting his hands and banging his head. Which of the following abnormalities is suspected?**

A. Deficiency of cystathionine β-synthase
B. Deficiency of guanosine triphosphate (GTP) cyclohydrolase 1
C. Deficiency of hypoxanthine–guanine phosphoribosyltransferase
D. Mutation in *ATP1A3*

**36. A newborn in the nursery has microcephaly. He also has ptosis, epicanthal folds, cleft palate, polydactyly, and ambiguous genitalia. His serum cholesterol level is low. What diagnostic test would support his diagnosis?**

A. Serum amino acids
B. Serum concentration of 7-dehydrocholesterol
C. Very-long-chain fatty acids
D. Urine organic acids

**37. In which disease(s) does lactate fail to increase as expected during forearm exercise testing?**

A. Phosphofructokinase deficiency
B. Myophosphorylase deficiency
C. Phosphoglycerate mutase deficiency
D. All of the above

**38. Enzyme replacement therapy is available for which of the following diseases?**

A. Gaucher disease
B. Fabry disease
C. Pompe disease (glycogen storage disease type II)
D. All of the above

**39. Which of the following findings help differentiate ataxia with vitamin E deficiency (AVED) from Friedreich ataxia (FA)?**

A. Nystagmus is present in FA but not in AVED.
B. Posterior column dysfunction is present in FA but not in AVED.
C. Cardiac conduction defects occur in FA but not in AVED.
D. Titubation is more common in FA.

**40. Which of the following improves with miglustat?**

A. Hyperornithinemia–hyperammonemia–homocitrullinuria (HHH) syndrome
B. Developmental delay, epilepsy, and neonatal diabetes (DEND) syndrome
C. Hyperekplexia
D. Niemann–Pick type C

**41. A neonate with encephalopathy and hyperammonemia has significant ketonuria. Which of the following conditions is most likely?**

A. β-Oxidation defect
B. HMG-CoA lyase deficiency
C. Hyperinsulinism–hyperammonemia
D. Organic aciduria
E. Urea cycle defect

**42. Which of the following is *least* likely to be associated with an elevated uric acid?**

A. HMG-CoA lyase deficiency
B. Hypoxanthine–guanine phosphoribosyltransferase (HPRT) deficiency
C. MCAD deficiency
D. Molybdenum cofactor deficiency

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# METABOLIC DISORDERS

## ANSWERS

### 1. C

Maple syrup urine disease (MSUD), which is a branched-chain aminoacidopathy, is least likely to cause hyperammonemia.

Some aminoacidopathies cause hyperammonemia, particularly those associated with urea cycle defects; however, some aminoacidopathies, such as MSUD, do *not* cause hyperammonemia.

Hyperammonemia can occur in patients with urea cycle defects, organic acidemias, and defects in fatty acid oxidation.

The urea cycle converts ammonia to urea and is involved in nitrogen elimination. Citrullinemia is caused by a urea cycle defect, which results in hyperammonemia.

Isovaleric acidemia is an organic acidemia that causes hyperammonemia.

Medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency is the most common fatty acid oxidation disorder. It can cause hyperammonemia.

### 2. C

Pyridoxine deficiency can cause refractory seizures in the neonatal period. A trial of oral or intravenous pyridoxine aids in the diagnosis of pyridoxine-dependent epilepsy. Intravenous pyridoxine can cause apnea, so it should be used with caution.

There is an increased risk for fatal hepatoxicity when valproic acid is used in patients younger than age 2 years.

### 3. B

Folinic acid–responsive seizures and pyridoxine-dependent epilepsy are allelic conditions. Both are caused by mutations in the *ALDH7A1* gene, which encodes α-aminoadipic semialdehyde dehydrogenase (AASDH), also known as antiquitin. AASDH/antiquitin is involved in lysine catabolism (the pipecolic acid pathway). Abnormalities in antiquitin/AASDH cause inactivation of pyridoxal phosphate, which results in seizures. α-Aminoadipic semialdehyde is increased in the plasma, urine, and CSF of these patients. In addition, pipecolic acid is elevated in the plasma and CSF.

Newborns with epilepsy who partially respond to pyridoxine and do not have a mutation in *ALDH7A1* may have a mutation in *PNPO*, which causes pyridoxal phosphate–responsive epilepsy. These patients respond to pyridoxal-5-phosphate.

### 4. C

This patient has MCAD deficiency, which is a disorder of fatty acid oxidation due to mutations in the *ACADM* gene. Hypoglycemia after a short fast suggests a defect in carbohydrate metabolism. Hypoglycemia after a prolonged fast suggests a disorder of fatty acid oxidation.

The enzyme MCAD participates in mitochondrial fatty acid β-oxidation, which is required for production of ketones in the liver. Hepatic ketogenesis is important during prolonged fasting and in conditions in which there are increased energy demands. Fasting should be avoid in patients with MCAD deficiency.

Classically, MCAD deficiency manifests in an infant or young child with vomiting and lethargy during an illness resulting in fasting. The child may have a seizure. Coma may occur. The patients often have hepatomegaly. Laboratory studies show hypoketotic hypoglycemia, hyperammonemia, and hyperuricemia. Plasma acylcarnitine testing aids in the diagnosis of MCAD deficiency.

MCAD deficiency, like some other fatty acid oxidation disorders, can also present with sudden death.[1]

Classic galactosemia manifests in the newborn period after exposure to breast milk or lactose-containing formula. This disorder of carbohydrate metabolism presents with feeding intolerance and liver dysfunction. These patients are at increased risk for *Escherichia coli* sepsis. Classic galactosemia is due to deficiency of galactose-1-phosphate uridyltransferase.

Lowe syndrome, or oculocerebrorenal syndrome, causes cataracts, hypotonia, and areflexia at birth. Patients have developmental delays and renal complications such as aminoaciduria and renal tubular acidosis. Lowe syndrome occurs primarily in males; it has an X-linked inheritance pattern.

Glycogen storage disease type V, or McArdle disease, causes a myopathy that manifests as exercise intolerance.

### 5. B

This patient has glutaric aciduria type I, which is an organic acidemia. It can manifest acutely at the time of illness or surgery, or it can occur as a chronic condition. Imaging may show bilateral widening of the Sylvian fissures, abnormal signal in the basal ganglia, bitemporal arachnoid cysts, or subdural hemorrhages. This is one of the mimickers of child abuse. Other neurologic diseases that are mimickers of child abuse include Menkes kinky hair disease and tuberous sclerosis complex.

Glutaric aciduria type I also causes macrocephaly. Other metabolic diseases that cause macrocephaly include Canavan disease, Alexander disease, and Tay–Sachs disease.

Glutaric acidemia type II, as opposed to type I, is caused by a defect in the electron transfer flavoprotein or the electron transfer flavoprotein dehydrogenase in the mitochondrial respiratory chain. It causes a defect in fatty acid and amino acid oxidation. It can result in metabolic crisis. Some of these patients have a "sweaty feet" odor. (Isovaleric acidemia also causes this type of odor.)

Cerebral folate deficiency manifests at approximately 4 months of age. It causes deceleration of head growth, epilepsy, irritability, ataxia, and dyskinesia. CSF levels of 5-methyltetrahydrofolate (5-MTHF) are low. It may be caused by mutations in *FOLR1*, which encodes folate receptor-α, or by autoantibodies against the folate receptor. It is treated with folinic acid (*not* folic acid, which can exacerbate the condition). Low CSF levels of 5-MTHF can also be found in other neurologic conditions, such as atypical Aicardi–Goutières syndrome, Rett syndrome, and mitochondrial encephalomyopathies.

Miller–Dieker syndrome is characterized by microcephaly, lissencephaly, distinctive facial features, and cardiac anomalies.

Mowat–Wilson syndrome causes microcephaly, distinctive facial features, Hirschsprung disease, and cardiac anomalies.

**6. B**

This child has PKU, which is an aminoacidopathy caused by phenylalanine hydroxylase deficiency. Children with PKU are microcephalic and have developmental delay, pale skin, pale hair, eczema, and a mousy/musty smell. In adulthood, patients can have hyperreflexia, tremor, paraplegia, or psychiatric conditions such as depression or anxiety.

There are other causes of hyperphenylalaninemia than PKU. Some of these are responsive to tetrahydrobiopterin, which is a cofactor for the hydroxylation reactions of phenylalanine, tyrosine, and tryptophan.

Biotinidase deficiency, sulfite oxidase deficiency, and PKU can all cause an eczematous rash.

Biotinidase deficiency causes alopecia; sulfite oxidase deficiency causes fine hair; and PKU causes fair hair and pale skin. Both biotinidase deficiency and sulfite oxidase deficiency can cause an epileptic encephalopathy.

Biotinidase deficiency is a type of multiple carboxylase deficiency. It causes seizures, hypotonia, developmental delay, and ataxia. Optic atrophy and hearing loss can occur. Alopecia, rash, and candidiasis are characteristic features. The rash is often perioral. Intermittent metabolic acidosis is seen, as well as lactic acidemia and propionic acidemia. Biotinidase deficiency is treated with biotin.

Sulfite oxidase deficiency may occur in isolation or as part of molybdenum cofactor deficiency. It causes microcephaly, failure to thrive, epilepsy, and lens dislocation. Lens dislocation is also seen in Marfan syndrome and homocystinuria (see Table 9.1).

**7. C**

This is maple syrup urine disease (MSUD). In the classic form of MSUD, the cerumen may have a sweet odor on the first day of life. If MSUD is left untreated, encephalopathy, abnormal movements (opisthotonus and bicycling), and seizures are seen, followed by coma and respiratory failure. MSUD is caused by a defect in branched-chain α-ketoacid dehydrogenase (BCKD). BCKD is required to break down leucine, isoleucine, and valine. Treatment is restriction of these three amino acids. One form of MSUD is responsive to thiamine.

**8. D**

This child has nonketotic hyperglycinemia (NKH), also known as glycine encephalopathy. NKH and molybdenum cofactor deficiency both cause seizures and a burst suppression pattern on EEG, but the history of hiccups is more typical of NKH.

NKH is a disorder of neurotransmitter degradation. In NKH, impaired glycine degradation results in accumulation of glycine in tissue. Most cases of NKH are due to mutations in *GLDC* or *AMT*, which encode components of the glycine cleavage enzyme system.[2] Treatments include sodium benzoate to reduce glycine levels and *N*-methyl-ᴅ-aspartate (NMDA) receptor antagonists such as dextromethorphan and ketamine. (Glycine is

*Table 9.1* FEATURES OF BIOTINIDASE DEFICIENCY, PHENYLKETONURIA, AND SULFITE OXIDASE DEFICIENCY

| | BIOTINIDASE DEFICIENCY | PHENYLKETONURIA | SULFITE OXIDASE DEFICIENCY |
|---|---|---|---|
| Skin | Eczema, perioral rash | Eczema, pale skin | Eczema |
| Hair | Alopecia | Light, blond hair | Fine hair |
| Neurologic features | Epileptic encephalopathy, hypotonia, developmental delay, ataxia, hearing loss | Microcephaly, developmental delay | Epileptic encephalopathy, microcephaly |
| Characteristic features | Candidiasis, episodic metabolic acidosis, lactic and propionic acidemia | Mousy/musty odor | Lens dislocation |

a co-agonist to glutamate at the NMDA receptor. In NKH, excess glycine can cause excitotoxity. In the spinal cord, glycine is usually inhibitory.) The ketogenic diet has also been used to treat NKH.[2,3]

Molybdenum cofactor is required for the function of sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase. Molybdenum cofactor deficiency causes an epileptic encephalopathy. Subtle dysmorphic features may be present. Sulfite, *S*-sulfocysteine, xanthine, and hypoxanthine are elevated in the urine. High levels of xanthine contribute to kidney stones. Serum uric acid is low. MRI shows brain edema followed by cystic lesions in the white matter. Patients with molybdenum cofactor deficiency type A can be treated with fosdenopterin (cyclic pyranopterin monophosphate).

The first step in serine synthesis requires 3-phospholycerate dehydrogenase. Deficiency of this enzyme causes intrauterine growth retardation, congenital microcephaly, and seizures in infancy reminiscent of a congenital infection.

**9. D**

This child has a congenital disorder of *N*-linked glycosylation, specifically PMM2-CDG. PMM2-CDG, which was formerly known as congenital disorder of glycosylation type Ia (CDG-Ia), is the most common disorder among this group of diseases.

PMM2-CDG is due to mutations in *PMM2*. The disease causes failure to thrive, developmental delay, and axial hypotonia. There may be cerebellar hypoplasia. Patients may have inverted nipples and fat pads in unusual locations (e.g., suprapubic and above the buttocks). Multiple systems may be affected. Transaminases are often elevated, and patients can have a coagulopathy or endocrine dysfunction. A pericardial effusion may be present. Transferrin isoform analysis supports the diagnosis, as does a low level of phosphomannomutase.

**10. D**

This patient has an organic acidemia. Examples of organic acidemias are glutaric acidemia type I, propionic acidemia, methylmalonic acidemia, multiple carboxylase deficiency, and isovaleric acidemia. Organic acidemias manifest with poor feeding, vomiting, lethargy, ketosis, acidosis, hyperammonemia, and neutropenia. The vomiting may be severe enough to be misdiagnosed as pyloric stenosis (i.e., in propionic acidemia, isovaleric acidemia, and methylmalonic acidemia). Hypoglycemia may be present. Patients with isovaleric acidemia may have a "sweaty feet" odor. MSUD may also be included in the organic acidemias, but it does not usually cause hyperammonemia or acidosis.

**11. A**

This child has Menkes disease, which is caused by mutations in the *ATP7A* gene, which encodes a transmembrane copper-transporting ATPase. Menkes disease is X-linked recessive. Newborns may have cephalohematomas, hypoglycemia, hypothermia, or inguinal hernias, but patients typically present with seizures, developmental delay or regression, and failure to thrive at a few months of age. Cheeks appear to sag; skin may be loose; and hair is sparse, friable, and resembles steel wool. Pili torti (twisted hair shafts) is a distinctive feature of Menkes disease. Patients are hypotonic. Wormian bones are seen in the cranial sutures. Brain MRI shows abnormal myelination and tortuous vessels. The patient may have subdural hematomas. Menkes disease can be mistaken for child abuse because of associated rib fractures and subdural hematomas.

Both Menkes disease and Wilson disease are caused by defects in copper-transporting ATPase. Wilson disease is caused by a mutation in the *ATP7B* gene on chromosome 13. In Menkes disease, there is a copper deficiency. Copper transport from the intestine into the blood is impaired. It is treated with copper replacement. In Wilson disease, there is excess copper. Copper excretion from the liver into the bile is impaired. It is treated with chelation. In both Menkes disease and Wilson disease, serum copper and ceruloplasmin are low. Liver copper is low in Menkes disease but high in Wilson disease (see Table 9.2).

*Table 9.2* COMPARISON OF MENKES DISEASE AND WILSON DISEASE

| MENKES DISEASE | WILSON DISEASE |
|---|---|
| **Copper deficiency** | **Copper excess** |
| **Defective absorption** | **Defective excretion** |
| **Treat with copper replacement** | **Treat with chelation** |

Mutations in the *OCRL* gene cause a defect in inositol polyphosphate 5-phosphatase OCRL-1. This results in oculocerebrorenal syndrome, also known as Lowe syndrome. As indicated by the name, patients have eye, brain, and kidney involvement. Patients have congenital cataracts and may have infantile glaucoma. At birth, patients are hypotonic with absent deep tendon reflexes. Development is delayed, and intellectual disability is common. Kidney involvement results in renal Fanconi syndrome. Lowe syndrome demonstrates X-linked inheritance.

Mutations in *PANK2* cause pantothenate kinase-associated neurodegeneration, which is a type of neurodegeneration with brain iron accumulation (NBIA).

Mutations in the *C19orf12* gene also cause a form of NBIA.

**12. B**

This is ornithine transcarbamylase deficiency, which is the most common urea cycle disorder. It is X-linked. In males, it can manifest in the newborn period with hyperammonemic coma. The presentation in females is typically less severe and is variable. Females may avoid protein and be asymptomatic. Recurrent vomiting is another presentation. Females may develop altered mental status and hyperammonemia at the time of illness. Valproic acid is also a trigger.

Hartnup disease is caused by mutations in the *SLC6A19* gene, which encodes a neutral amino acid transporter expressed in the proximal renal tubules and in the intestine. Patients with Hartnup disease have pellagra-like skin changes and neurologic or psychiatric symptoms. Intermittent recurrent ataxia is one of the major neurologic manifestations.

Tangier disease is associated with reduced levels of high-density lipoprotein in the blood. Cholesterol esters accumulate in tissues. Patients have premature atherosclerosis, orange tonsils, neuropathy, lymphadenopathy, and hepatosplenomegaly. They may also have corneal opacities.

Wolman disease, which is caused by lysosomal acid lipase deficiency, results in deposition of fat in multiple organs. Calcified adrenal glands are characteristic of the disorder.

**13. B**

Mucopolysaccharidoses (MPS) are a type of lysosomal storage disease. In MPS, glycosaminoglycans are stored in tissue and found in urine.

Patients with MPS are at risk for odontoid hypoplasia and cord compression, hydrocephalus, carpal tunnel syndrome, and obstructive sleep apnea. (Patients with trisomy 21 also have atlantoaxial instability and an increased risk for obstructive sleep apnea.) Seizures may occur with MPS type IIIA (Sanfilippo syndrome A).

There are many types of MPS. Skeletal defects are typical; dysostosis multiplex is characteristic. Many types are associated with cognitive impairment, cloudy corneas, hearing loss, coarse facial features, short stature, heart disease, and hepatosplenomegaly. Hunter syndrome, which is X-linked, is not associated with corneal clouding. Retinal degeneration may occur in some types. Enlarged perivascular spaces are often seen on brain MRI in patients with MPS.

In addition to MPS, the lysosomal storage diseases include glycogen storage disease type II, lipidoses, mucolipidoses, oligosaccharidoses/glycoproteinoses, and sphingolipidoses (see Box 9.1).

***Box 9.1*** **TYPES OF LYSOSOMAL STORAGE DISEASES**

- Glycogen storage disease type II (Pompe disease)
- Lipidoses (neuronal ceroid lipofuscinoses, Niemann–Pick disease types C and D, Wolman disease)
- Mucolipidoses
- Mucopolysaccharidoses
- Oligosaccharidoses/glycoproteinoses
- Sphingolipidoses

**14. B**

CSF protein is increased in this condition. This patient has metachromatic leukodystrophy (MLD), which is a lysosomal storage disease. It is a disorder of sphingolipid metabolism.

The late infantile form is the most common form of MLD. It manifests between 1 and 2 years of age. Symptoms may appear to begin after an infection or anesthesia. Patients have motor regression. Reflexes are decreased, but there is an extensor plantar response. Initially, patients with MLD may be hypotonic, but they develop spastic quadriplegia and optic atrophy resulting in blindness. The patient may have seizures. Intestinal bleeding and gallbladder papillomatosis can occur with MLD. MRI shows bilateral, symmetric signal changes in the periventricular white matter with sparing of the U fibers. Patients have a demyelinating neuropathy resulting in slowed nerve conduction velocities and prolonged F-waves. Laboratory studies show an increase in urine sulfatide excretion. Nerve and brain biopsies show metachromatic lipid deposits. Arylsulfatase A is decreased.

If the patient has the MLD phenotype but arylsulfatase A activity is normal, then the patient may have saposin B deficiency. Saposin B acts as a cerebroside sulfatase activator.

There are milder adult forms of MLD that manifest with psychiatric or motor symptoms.

Multiple sulfatase deficiency manifests similar to MLD, but the patient also has features of MPS as well as ichthyosis. Sulfatide and MPS are increased in the urine of patients with multiple sulfatase deficiency.

Like MLD, Krabbe disease can also cause elevated CSF protein and delayed nerve conduction velocities. Nerve specimens from patients with Krabbe disease and MLD contain deposits of sphingolipids.

**15. D**

This is X-linked adrenoleukodystrophy (ALD), which is the most common peroxisomal disorder. Very-long-chain fatty acids are elevated in ALD. The gene responsible for ALD is *ABCD1* (ATP-binding cassette, subfamily D, member 1).

This patient has the childhood cerebral form of X-linked ALD. It manifests in school-age children with symptoms resembling those of ADHD. Patients eventually develop dementia, visual and hearing impairments, quadriplegia, and adrenal insufficiency. MRI shows symmetric involvement of the posterior periventricular white matter. Garland-like contrast enhancement may be present at the periphery of the signal abnormality. Lorenzo's oil and stem cell transplant were used as treatments. In 2022, elivaldogene autotemcel was approved by the U.S. Food and Drug Administration for males with early, active cerebral ALD. Per the package insert, this gene therapy "adds functional copies of the ABCD1 cDNA into patients' hematopoietic stem cells (HSCs) through transduction of autologous CD34$^+$ cells with Lenti-D LVV [lentiviral vector]."[4] Risks of this treatment include hematologic malignancies.

Adrenomyeloneuropathy is another form of X-linked ALD. It manifests in the third decade of life with progressive spastic paraparesis and adrenal insufficiency.

X-linked ALD may also manifest as Addison disease without neurologic symptoms (initially).

Neonatal ALD is a different entity. Neonatal ALD is one of the peroxisome biogenesis disorders, Zellweger syndrome spectrum. These disorders are autosomal recessive and are caused by mutations in *PEX* genes.

## 16. B

Very-long-chain fatty acids, phytanic acid, pristanic acid, and pipecolic acid aid in diagnosis of the Zellweger syndrome spectrum of peroxisome biogenesis disorders, which includes Zellweger disease, neonatal ALD, and infantile Refsum disease. These diseases are caused by mutations in *PEX* genes. *PEX* genes encode peroxins, which are required for normal peroxisome assembly.

Zellweger syndrome is the most severe form, neonatal ALD is the intermediate form, and infantile Refsum disease is the least severe form.

Zellweger syndrome manifests in the newborn period with hypotonia, seizures, and poor feeding. Patients with Zellweger syndrome may have polymicrogyria, heterotopia, subependymal cysts, or a hypoplastic corpus callosum. Patients have a large fontanelle, a high forehead, flattened facies, a flat occiput, epicanthal folds, and a broad nasal bridge. There may be redundant skin folds on the neck. Some cases have been misdiagnosed as Down syndrome. Multiple systems are involved. Patients with Zellweger syndrome can have hepatic dysfunction, renal cysts, and chondrodysplasia punctata (bony stippling) of the patellae.

Like patients with Zellweger syndrome, patients with neonatal ALD have hypotonia and may have seizures, but they are less likely to have cortical malformations and craniofacial abnormalities. In addition, stippled epiphyses are more characteristic of Zellweger syndrome.

Infantile Refsum disease is even less severe and may not manifest until later in life.

Patients with diseases in the Zellweger syndrome spectrum are at risk for coagulopathy and can develop intracranial hemorrhage.

Zellweger syndrome spectrum is one of two groups of peroxisome biogenesis disorders. Rhizomelic chondrodysplasia punctata type 1 is in the other group.

Palmitoyl-protein thioesterase 1 (PPT-1) is deficient in CLN1, one of the types of neuronal ceroid lipofuscinoses (NCLs). CLN2 (classic late infantile NCL) is caused by mutations in *TPP1*, which encodes tripeptidyl-peptidase 1. Cerliponase alfa (an enzyme replacement therapy) is a treatment for CLN2. Mutations in *CSTD*, which encodes cathepsin D, cause CLN10.

## 17. A

This is Alexander disease, which is a leukodystrophy. The infantile form is the most common form. Patients have developmental regression, macrocephaly, and spasticity. Some patients have seizures. Brain MRI shows increased T2 signal in the cerebral white matter with frontal predominance. Signal abnormality may also be seen in the basal ganglia and in the brainstem. Some patients have aqueductal stenosis and develop hydrocephalus. Alexander disease is caused by defects in the *GFAP* gene, which encodes the glial fibrillary acidic protein and is autosomal dominant. Mutations in the *GFAP* gene result in an abnormal glial fibrillary acidic protein that forms Rosenthal fibers within astrocytes. (Rosenthal fibers are also seen in pilocytic astrocytoma.)

Alexander disease can cause brainstem lesions that resemble a tumor. It can also mimic multiple sclerosis.

*PCDH19* mutations cause an early infantile epileptic encephalopathy in females. (It is found on the X chromosome.)

*STXBP1* mutations cause another early infantile epileptic encephalopathy.

*PRICKLE1* mutations cause a progressive myoclonic epilepsy (EPM1B) with ataxia; however, intellect is spared.

## 18. D

Mutations in the proteolipid protein 1 (*PLP1*) gene cause Pelizaeus–Merzbacher disease. Proteolipid protein is a component of myelin in the central nervous system.

Pelizaeus–Merzbacher disease is an X-linked recessive hypomyelinating disorder. Classic Pelizaeus–Merzbacher disease manifests with nystagmus in the first few months of life, stridor, and hypotonia. Patients then develop titubation, ataxia, and spasticity. Athetosis may be present.

MRI shows persistent hypomyelination without significant cortical atrophy. Alternating areas of myelination (around penetrating vessels) and demyelination may produce a "tigroid" appearance. (This can be seen in other conditions as well.) Pelizaeus–Merzbacher disease has a distinct pattern on magnetic resonance spectroscopy that helps differentiate it from other demyelinating conditions.

There is a severe connatal form of Pelizaeus–Merzbacher disease that manifests at birth or within the first few weeks of life.

Mutations in gene *PLP1* also cause spastic paraplegia 2 (SPG2).

β-Galactosidase deficiency causes GM1 gangliosidosis. The most severe form is the infantile form, which manifests by 1 year of age with developmental regression and hypotonia. The patient may have an exaggerated startle. Patients develop a macular cherry-red spot, facial coarsening, hypertrophic gums, macroglossia, hepatosplenomegaly, scoliosis, and dysostosis. Some patients have mild corneal clouding. Some have cardiomyopathy.

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Ultimately, patients lose vision and develop seizures, decerebrate rigidity, and beaked vertebral bodies.

**19. B**

This is childhood ataxia with central nervous system hypomyelination/vanishing white matter (CACH/VM), also known as leukoencephalopathy with vanishing white matter. There are variable forms, and it can manifest at multiple ages. It may manifest with ataxia or spasticity. Some patients have optic atrophy. A distinct feature is significant deterioration occurring after minor head trauma or infection. Patients may have seizures, hypotonia, and vomiting and may become comatose in these settings. Brain MRI shows progressive white matter destruction with replacement by CSF. CSF asialotransferrin is decreased. CACH/VM is caused by mutations in the genes encoding subunits of the eIF2B.

**20. A**

The condition is Aicardi–Goutières syndrome.

Some patients with Aicardi–Goutières syndrome are normal initially. They later present with encephalopathy, irritability, and sterile pyrexia. Loss of milestones occurs. Patients develop spasticity and microcephaly. They may have seizures or dystonia. Some patients develop chilblain lesions on the digits. MRI shows calcifications in the basal ganglia, cerebral atrophy, and increased T2 signal in the white matter. CSF shows increased interferon-α or lymphocytosis.

Some patients with Aicardi–Goutières syndrome have a presentation similar to that of a patient with a congenital infection. They have fever, hepatosplenomegaly, elevated liver function enzymes, and thrombocytopenia at birth.

Aicardi–Goutières syndrome results from mutations in genes encoding nucleases. For example, mutations in the *TREX1* gene are one cause of Aicardi–Goutières syndrome. Mutations in this gene also cause retinal vasculopathy with cerebral leukodystrophy, chilblain lupus, and susceptibility to systemic lupus erythematosus.

Kearns–Sayre syndrome is a mitochondrial disease characterized by ptosis, progressive external ophthalmoplegia, and pigmentary retinopathy. Patients may have dementia, ataxia, cardiac conduction defects, sensorineural hearing loss, or endocrine abnormalities (e.g., diabetes). Blood and CSF lactate levels may be elevated. CSF protein is often elevated. MRI shows increased signal in the subcortical white mater and may show cerebral, brainstem, or cerebellar atrophy. Patients may have calcifications in the basal ganglia. Magnetic resonance spectroscopy shows elevated lactate.

In patients with megalencephalic leukoencephalopathy with subcortical cysts, the white matter is abnormal diffusely and cysts are consistently found in the anterior temporal region but may be found elsewhere as well.

Hereditary diffuse leukoencephalopathy with spheroids is a genetic leukoencephalopathy that can mimic multiple sclerosis.

**21. B**

Cerebrotendinous xanthomatosis is a disorder of lipid storage. Specifically, bile acid synthesis is defective because of a mutation in the gene that encodes sterol 27-hydroxylase. It may manifest with neonatal cholestasis, chronic diarrhea, or cataracts. During adolescence and young adulthood, tendon xanthomas appear. They are often found on the Achilles tendon. Patients have premature atherosclerosis and neurologic deterioration. They develop spasticity and ataxia. Some may have neuropsychiatric symptoms (including dementia), peripheral neuropathy, or seizures. MRI shows cerebellar white matter hyperintensity. The dentate may demonstrate T2 hyperintensity or hypointensity. Treatment is chenodeoxycholic acid.

Adult-onset polyglucosan body disease causes upper and lower motor neuron symptoms and can be clinically mistaken for amyotrophic lateral sclerosis. Brain MRI shows white matter abnormalities that can be mistaken for multiple sclerosis.

HMG-CoA lyase deficiency and L2-hydroxyglutaric aciduria are other genetic leukoencephalopathies that can cause multifocal white matter lesions mimicking multiple sclerosis.

**22. B**

This patient has Krabbe disease, which is also known as globoid cell leukodystrophy. It is a lysosomal storage disease, specifically a sphingolipidosis. It results from a deficiency of galactocerebrosidase (also known as galactosylceramidase or galactosylceramide β-galactosidase), which is caused by mutations in *GALC*. Most patients with Krabbe syndrome present by 6 months of age with irritability, sensitivity to external stimuli, and fever without infection. Patients have spasticity and vision loss. Krabbe disease affects the white mater of the central and peripheral nervous systems, causing leukodystrophy and a peripheral neuropathy. Multinucleated globoid cells are found in the white matter of the brain. Like MLD, Krabbe disease can cause elevated CSF protein and delayed nerve conduction velocities. In Krabbe disease, psychosine is elevated and galactocerebrosidase activity is decreased.

Ceramidase deficiency causes Farber disease, which is also known as Farber lipogranulomatosis. This is a sphingolipidosis and one cause of a macular cherry-red spot.

Sphingomyelinase deficiency causes Niemann–Pick disease types A and B, which are also sphingolipidoses. The sphingolipidoses also include Fabry disease, Gaucher disease, GM1 gangliosidoses, multiple sulfatase deficiency, Sandhoff disease, and Tay–Sachs disease (see Box 9.2).

*Box 9.2* SPHINGOLIPIDOSES

- Fabry disease
- Farber disease
- Gaucher disease
- GM1 gangliosidosis
- GM2 gangliosidoses (Sandhoff disease and Tay–Sachs disease)
- Krabbe disease
- Metachromatic leukodystrophy
- Multiple sulfatase deficiency
- Niemann–Pick disease types A and B

Neuraminidase deficiency causes sialidosis type I, which is discussed later.

**23. B**

This patient has Gaucher disease type 2, which is one of the sphingolipidoses. It is caused by a mutation in *GBA*, which results in glucocerebrosidase (glucosylceramidase) deficiency. Patients have bulbar signs such as stridor and dysphagia, pyramidal signs such as opisthotonus and spasticity, and oculomotor abnormalities such as strabismus. Squinting and oculomotor apraxia may also be seen. Trismus can occur. Patients may have seizures. Hepatosplenomegaly is present. Gaucher cells may be seen in the bone marrow.

AADC deficiency, which is an inborn error in neurotransmitter metabolism, can also cause opisthotonus and hyperreflexia. It leads to oculogyric crises and can cause autonomic dysfunction. Hepatosplenomegaly would not be expected.

GAMT deficiency, SLC6A8 deficiency, and L-arginine:glycine amidinotransferase (AGAT or GATM) deficiency are cerebral creatine deficiency syndromes. They are characterized by seizures and intellectual disability. Patients with GAMT deficiency may also have autistic behaviors and dystonia. Some demonstrate self-mutilation.

**24. B**

Canavan disease is a leukodystrophy caused by aspartoacylase deficiency. Infants with Canavan disease present with developmental delay. They have macrocephaly, head lag, and hypotonia. Later, spasticity develops. Urine *N*-acetyl aspartate (NAA) is elevated. MRI shows bilateral diffuse white matter involvement including the U fibers (increased signal on T2 and decreased signal on T1). Magnetic resonance spectroscopy shows an elevated NAA peak.

**25. B**

This patient has Tay–Sachs disease, which is a lysosomal storage disease. Specifically, it is a type of GM2 gangliosidosis. It is caused by deficiency in hexosaminidase A. Patients present with increased startle. Initially, they are weak and hypotonic. Later, they become hypertonic, macrocephalic, and blind. Patients also have seizures and a macular cherry-red spot.

Sandhoff disease, which is also a type of GM2 gangliosidosis, is caused by deficiency of hexosaminidase A and B. It has neurologic features similar to those of Tay–Sachs disease, including a cherry-red spot. However, hepatosplenomegaly occurs in Sandhoff disease, whereas patients with Tay–Sachs disease have normal-sized organs. Patients with Sandhoff disease may also have bony abnormalities.

**26. A**

This is Fabry disease, which is a X-linked lysosomal disease caused by deficiency of α-galactosidase A. This results in accumulation of glycosphingolipids, specifically globotriaosylceramide, in cells. (Fabry disease is the only X-linked sphingolipidosis.) Patients with Fabry disease are at risk for early stroke, usually in the vertebrobasilar circulation. Fabry disease is also associated with dolichoectasia of cerebral vessels, white matter abnormalities, cardiac conduction defects, and cardiomyopathy. In addition, it causes a small-fiber peripheral neuropathy and autonomic dysfunction. Patients have hypohidrosis, painful acroparesthesias, and intestinal dysmotility. Other systemic manifestations include renal failure and corneal opacities. Angiokeratomas are one of the earliest findings. Enzyme replacement therapy is available.

**27. A**

This patient has Niemann–Pick type C disease, which is a lysosomal lipid storage disease caused by impaired cholesterol esterification. Clinical features include cataplexy, dysarthria, dementia, vertical gaze palsy, ataxia, seizures, and hepatosplenomegaly. Movement disorders including dystonia, chorea, athetosis, and parkinsonism also occur in Niemann–Pick type C disease. Foam cells, which stain with filipin, and sea-blue histiocytes may be found in bone marrow.

**28. B**

This patient has classic late infantile neuronal ceroid lipofuscinosis (CLN2), which causes progressive myoclonic epilepsy. Curvilinear profiles are found within lysosomes.

NCLs are a type of lysosomal storage disease. There are multiple types, which manifest at different ages. Patients with NCL have seizures and regress in motor skills and cognition. Often, they have vision impairment as well.

CLN1 (infantile NCL) is caused by mutations in *PPT1*, which encodes palmitoyl-protein thioesterase 1. Granular osmiophilic deposits are found within lysosomes. These are seen in some other forms of NCL as well.

CLN2 is caused by mutations in *TPP1*, which encodes tripeptidyl-peptidase 1. Cerliponase alfa is an intrathecal

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medication used to treat neuronal ceroid lipofuscinosis type 2 due to deficiency of tripeptidyl-peptidase 1.

CLN3 (classic juvenile NCL) manifests in school-age children. Fingerprint profiles are found within lysosomes.

Ragged red fibers are found on muscle biopsy in mitochondrial diseases.

Electron-dense granules within the smooth muscle layer of small arterial vessels are found in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).

Spheroids are found on nerve biopsy in patients with infantile neuroaxonal dystrophy.

**29. C**

Sialidosis type I, Lafora body disease, NCLs, and Unverricht–Lundborg disease all cause progressive myoclonic epilepsy. In addition to progressive myoclonic epilepsy, patients with sialidosis type I have a cherry-red spot and progressive vision loss. Sialidosis type I is caused by deficiency of neuraminidase. It is a type of lysosomal storage disease. Specifically, it is one of the oligosaccharidoses/glycoproteinoses.

A number of other diseases can cause a cherry-red spot, including Niemann–Pick type A disease, Sandhoff disease, and Tay–Sachs disease.

Marinesco–Sjögren syndrome is characterized by cataracts, cerebellar ataxia, and myopathy.

**30. B**

This patient has myoclonic epilepsy associated with ragged red fibers (MERRF), which is a progressive myoclonic epilepsy. Most commonly, it is caused by mutations in the mitochondrial DNA gene *MT-TK*, which encodes $\text{tRNA}^{\text{Lys}}$. Wolff–Parkinson–White syndrome and cardiomyopathy can occur in MERRF. Patients may also have dementia, myopathy, polyneuropathy, ataxia, hearing loss, optic atrophy, short stature, and lipomas. Lactate is elevated.

Aggregates of polyglucosan (long, insoluble strands of glycogen) in the apocrine and eccrine glands are found on skin biopsy of patients with Lafora disease with the use of periodic acid–Schiff staining. Lafora disease is another progressive myoclonic epilepsy. It is caused by mutations in either the *EPM2A* gene, which encodes laforin, or the *NHLRC1* gene (previously known as *EPM2B*), which encodes malin. Lafora disease manifests in adolescence. Visual seizures are often the first sign. In addition to focal seizures arising from the occipital region, patients have generalized tonic–clonic and myoclonic seizures. Dementia occurs early.

**31. D**

Classic glucose transporter type 1 deficiency syndrome (Glut1-DS) manifests as refractory epilepsy in infants. The preprandial EEG may be worse than the postprandial EEG. CSF glucose is low compared with serum glucose. If Glut1-DS is left untreated, it causes microcephaly, developmental delays, and movement disorders. The gene responsible for Glut1-DS is *SLC2A1*, which stands for solute carrier family 2 (facilitated glucose transporter), member 1. *SLC2A1* encodes a glucose transporter in the blood–brain barrier. In addition to causing refractory epilepsy in infants, mutations in *SLC2A1* can cause early onset absence epilepsy, alternating hemiplegia of childhood, paroxysmal choreoathetosis with episodic ataxia and spasticity (DYT9), and epilepsy with exercise-induced dyskinesia (DYT18).

The gene *CACNA1A* encodes the calcium channel, voltage-dependent, P/Q type, $\alpha_{1A}$ subunit. Mutations in *CACNA1A* cause episodic ataxia type 2, familial hemiplegic migraine type 1, and spinocerebellar ataxia type 6.

Mutations in *GABRAG2*, which encodes the $\gamma$-aminobutyric acid receptor type A $\gamma_2$ subunit, are one cause of childhood absence epilepsy.

Mutations in the *PLA2G6* gene, which encodes A2 phospholipase, cause infantile neuroaxonal dystrophy. Mutations in this gene also cause neurodegeneration with brain iron accumulation type 2B and Parkinson disease type 14.

**32. D**

The ketogenic diet is used to treat Glut1-DS.

Sulfonylurea has been used in the treatment of developmental delay, epilepsy, and neonatal diabetes, which is caused by a potassium channel mutation.

**33. C**

This patient has Leigh syndrome, which is also known as subacute necrotizing encephalomyelopathy. There are several genetic causes of Leigh syndrome. Most gene mutations affect energy production in the mitochondria. Mutations in *SURF1*, which cause disruption of the cytochrome *c* oxidase complex, are the most common nuclear gene mutations that cause Leigh syndrome. (The most common mutations in nuclear DNA that cause Leigh syndrome cause disruption of cytochrome oxidase [COX], which is complex IV. Mutations in the gene *SURF1* are the most common cause of Leigh syndrome due to COX deficiency.) Leigh syndrome can also be caused by mutations in mitochondrial DNA, most commonly *MT-ATP6*, which encodes the ATP synthase protein complex (complex V). Defects in pyruvate dehydrogenase complex and other enzymes involved in energy production also cause Leigh syndrome.

Leigh syndrome is a neurodegenerative condition that usually manifests before 1 year of age, often at the time of a viral infection. Patients have seizures, hypotonia, developmental delay, failure to thrive, and vomiting. Patients also have psychomotor regression and develop movement disorders, ophthalmoplegia, peripheral neuropathy, respiratory disturbances, and swallowing dysfunction. Some patients have epilepsy. MRI shows symmetric necrosis in the thalamus, basal ganglia, and brainstem. Lactate is elevated.

Idiopathic basal ganglia calcification-1 (IBGC1), formerly known as Fahr disease, typically manifests in adulthood but can occur in the second decade of life. It causes parkinsonism and choreoathetosis. Some patients have hypoparathyroidism. IBGC1 is caused by a mutation in the *SLC20A2* gene, which encodes a phosphate transporter.

Kernicterus, or bilirubin encephalopathy, causes choreoathetoid cerebral palsy, vertical gaze disturbance, and hearing loss.

NBIA includes multiple disorders characterized by the accumulation of iron in the basal ganglia. This results in symptoms such as parkinsonism, dystonia, and choreoathetosis. Most types of NBIA are autosomal recessive. However, β-propeller protein–associated neurodegeneration (BPAN), which is caused by mutations in *WDR45*, is X-linked dominant. Also, neuroferritinopathy, caused by mutations in *FTL*, is autosomal dominant.

Pantothenate kinase–associated neurodegeneration (PKAN) is the most common form of NBIA. It is caused by mutations in the gene *PANK2*. It produces an "eye of the tiger" sign on MRI. There is decreased T2 signal in the globus pallidus and substantia nigra, with an area of hyperintensity in the center.

**34. B**

Valproic acid is contraindicated in patients with hepatic disease, urea cycle defects, and mitochondrial disease. Valproic acid can cause liver failure and death in patients with mutations in the mitochondrial DNA polymerase-γ (POLG) gene. POLG conditions include Alpers–Huttenlocher syndrome, childhood myocerebrohepatopathy spectrum disorders, myoclonic epilepsy myopathy sensory ataxia, POLG-related ataxia neuropathy spectrum disorders, and progressive external ophthalmoplegia.

Valproic acid is safe to use in patients with Dravet syndrome who have a *SCN1A* mutation and in patients with type II hyperprolinemia. It is also safe to use in patients with autosomal dominant nocturnal frontal lobe epilepsy caused by a mutation in *CHRNA2*; however, these patients are often treated with oxcarbazepine or carbamazepine.

**35. C**

This is Lesch–Nyhan disease, which is a disorder of purine metabolism. It is an X-linked recessive condition caused by a mutation in the *HPRT1* gene. Initially, patients with Lesch–Nyhan disease have hypotonia and developmental delay. Later, they develop spasticity, extrapyramidal movements (e.g., choreoathetosis or dystonia), and self-mutilating behaviors. Patients often have cognitive impairment. Uric acid is elevated in blood and urine, and hypoxanthine–guanine–phosphoribosyltransferase (HGPRT) levels are low. Excess uric acid can cause arthritis and kidney and bladder stones. Orange crystals may be seen in the diaper of babies with Lesch–Nyhan disease.

Cystathionine β-synthase deficiency is a cause of homocystinuria, which is a disorder of sulfur amino acid metabolism. Homocystinuria is associated with a Marfanoid body habitus, intellectual delay, downward lens dislocation, and increased risk for thromboembolism. Some cases of homocystinuria respond to pyridoxine (B6).

Deficiency of GTP cyclohydrolase 1 causes dopa-responsive dystonia.

Mutations in *ATP1A3* cause rapid-onset dystonia–parkinsonism (DYT12), alternating hemiplegia of childhood 2, an epileptic encephalopathy, and CAPOS syndrome (cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss).

**36. B**

The clinical and laboratory findings in this patient are suggestive of Smith–Lemli–Opitz syndrome, which is a condition associated with multiple congenital anomalies such as cleft palate, cardiac defects, ambiguous genitalia, postaxial polydactyly, and syndactyly of the second and third toes. Patients have growth retardation, microcephaly, and intellectual disability. Patients can have a range of central nervous system abnormalities, such as malformations of the cerebellum, corpus callosum malformation, Dandy–Walker malformation, or holoprosencephaly. Smith–Lemli–Opitz syndrome is caused by abnormal cholesterol metabolism resulting from a deficiency of 7-dehydrocholesterol (7-DHC) reductase. This leads to elevated levels of 7-DHC in the serum. Cholesterol is often low, but it can be in the normal range.

This syndrome does share some features with trisomy 13 and trisomy 18. Like patients with trisomy 13, patients with Smith–Lemli–Opitz syndrome can have holoprosencephaly, cleft palate, cardiac defects, and polydactyly; however, they also have ambiguous genitalia and may have a low serum cholesterol level. Patients with Smith–Lemli–Opitz syndrome may also have photosensitivity.

Other metabolic conditions that cause photosensitivity include phenylketonuria, Hartnup disease, and porphyria. Patients with Cockayne syndrome, ataxia–telangiectasia, xeroderma pigmentosum, and Bloom syndrome also have photosensitivity. Pellagra is a nutritional disorder that causes photosensitivity.

**37. D**

Patients with phosphofructokinase deficiency or myophosphorylase deficiency do not have a rise in lactate during forearm testing. Patients with phosphoglycerate mutase deficiency have reduced lactate elevation.

(Ischemia is no longer included in forearm exercise testing.)

**38. D**

Enzyme replacement therapy is available for Fabry disease (α-galactosidase A deficiency), Gaucher disease (glucocerebrosidase deficiency), Pompe disease (acid maltase deficiency), and certain mucopolysaccharidoses.

**39. C**

Ataxia with vitamin E deficiency (AVED) has also been called Friedreich-like ataxia. Given that AVED is treatable, it is important to differentiate it from FA. Cardiac conduction defects, cavus foot deformity, muscle weakness, and diabetes mellitus are more likely in FA than in AVED. Patients with AVED are more likely to have titubation.

**40. D**

Miglustat is a glucosylceramide synthase inhibitor. This enzyme is involved in the first step in the synthesis of many glycosphingolipids. It is used to treat Niemann–Pick type C and Gaucher disease. The neurological symptoms of Niemann–Pick type C improve with miglustat, but it does not help the neurological symptoms of patients with Gaucher disease.

Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome is a disorder of mitochondrial ornithine transport due to *SLC25A15* mutations. It causes spastic paraparesis. It can also cause liver dysfunction and coagulopathy.[5]

Developmental delay, epilepsy, neonatal diabetes (DEND) syndrome is a potassium channelopathy; it is due to mutations in a potassium channel gene (*KCNJ11*). Patients with this condition may benefit from treatment with sulfonylurea.

Clonazepam is a treatment for hyperekplexia.

**41. D**

Ketonuria and hyperammonemia in a neonate should raise concern for an organic aciduria. Organic acidurias can also cause acidosis and an elevated lactic acid. The patient may have hypoglycemia. An elevated uric acid also can be seen in organic acidurias.

Patients with β-oxidation defects can have hyperammonemia, but these patients tend to have hypoglycemia *without* ketonuria.

HMG-CoA lyase deficiency and urea cycle defects can cause hyperammonemia, but they usually do *not* cause ketonuria.[5]

Hyperinsulinism–hyperammonemia is due to mutations in the gene that encodes glutamate dehydrogenase. Ketonuria is *not* usually present.[5] Persistent hyperinsulinism may be treated with diazoxide.

**42. D**

Molybdenum cofactor deficiency tends to be associated with a *low* uric acid.

HMG-CoA lyase deficiency, HPRT deficiency, and MCAD deficiency can be associated with an *elevated* uric acid level. As mentioned above, an elevated uric acid can occur in organic acidemias as well.

Patients with HMG-CoA lyase deficiency cannot metabolize leucine or make ketones.

HPRT is an enzyme involved in purine metabolism. Deficiency of HPRT causes Lesch–Nyhan disease.

An elevated uric acid can be seen in β-oxidation defects, such as MCAD deficiency.[5]

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# 10.

# MOVEMENT DISORDERS

## QUESTIONS

1. **The subthalamic nucleus activates which inhibitory structure?**
   A. Globus pallidus internal segment
   B. Nucleus accumbens
   C. Striatum
   D. Thalamus

2. **Fill in the blank: In the basal ganglia direct pathway, the striatum sends GABAergic projections to the __________________.**
   A. Globus pallidus externa
   B. Globus pallidus internal segment and substantia nigra pars reticularis
   C. Subthalamic nucleus
   D. Thalamus

3. **Fill in the blank: The basal ganglia indirect pathway involves __________________ and then the __________________.**
   A. The globus pallidus externa and then the subthalamic nucleus
   B. The globus pallidus interna and then the subthalamic nucleus
   C. The substantia nigra pars compacta and then the substantia nigra pars reticularis
   D. The raphe nucleus and then the substantia nigra pars compacta

4. **A 2-year-old with no past medical history and normal development presents with episodes of arm flapping. These occur when she is anxious, bored, or excited. Her parents can distract her from them, and they do not occur in sleep. Her exam is normal. What is the most likely diagnosis?**
   A. Athetosis
   B. Chorea
   C. Myoclonus
   D. Stereotypy

5. **Which of the following disorders is most likely to occur during action rather than during rest?**
   A. Chorea
   B. Paroxysmal nonkinesigenic dyskinesia (PNKD)
   C. Stereotypies
   D. Tics

6. **Which is the most accurate term for the occurrence of an unintentional movement along with a voluntary movement?**
   A. Athetosis
   B. Overflow
   C. Myoclonus
   D. Ballism

7. **Which of the following descriptions is more characteristic of rigidity than spasticity?**
   A. There is velocity-independent resistance to passive movement.
   B. It has a "clasp-knife" quality.
   C. It affects upper extremity flexors more than extensors.
   D. Resistance is delayed if the direction of passive movement is reversed rapidly.

8. **Which of the statements about tics is *false*?**
   A. Tics can be temporarily suppressed but tend to increase after a period of suppression.
   B. They can occur during sleep.
   C. They are usually rhythmic.
   D. They are suggestible.

9. **A 10-year-old boy with a history of attention-deficit/hyperactivity disorder (ADHD) is brought to the clinic for unusual movements and noises. Two years ago, he began making sniffing noises and clearing his throat. Allergy medications did not work. He then started blinking his eyes. His eye examination was normal. During the visit, he intermittently shrugs his shoulders for no apparent reason. He says he can stop it briefly, but then it is worse when it restarts. Which other condition is the patient most likely to have?**
   A. Delusions
   B. Hallucinations
   C. Obsessive–compulsive disorder
   D. Panic attacks

10. **Which of the following is *not* required for the diagnosis of Tourette syndrome?**
    A. Onset before age 18 years
    B. Coprolalia
    C. Duration of at least 1 year
    D. At least one vocal tic

11. **An 11-year-old boy with Tourette syndrome is having significant difficulties in school due to ADHD and problems with impulse control. His tics are mildly distressing to him. Which of the following medications is most likely to treat all of his symptoms and be most helpful to him?**
    A. Atomoxetine
    B. Clonidine

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C. Fluphenazine
D. Risperidone

**12. A 59-year-old man presents with right-hand tremor. On examination, the patient has bradykinesia, cogwheel rigidity, a resting tremor, and reduced arm swing when walking. When he reaches a doorway or needs to turn, he freezes. Which of the following findings is expected?**
A. Decreased pigmented neurons in the substantia nigra
B. Loss of neurons in the substantia nigra pars compacta that are immunoreactive with tyrosine hydroxylase
C. Intraneuronal inclusions that immunostain with antibodies to α-synuclein
D. All of the above

**13. Which of the following features suggests that a patient may have a diagnosis other than Parkinson disease (PD)?**
A. Asymmetric tremor
B. Early gait instability
C. Tremor improves with action
D. Tremor worsens with mental tasks

**14. What is the function of carbidopa?**
A. It inhibits aromatic amino acid decarboxylase.
B. It results in increased dopamine synthesis.
C. It causes dopamine release.
D. It prevents dopamine metabolism.

**15. Which of the following side effects is more likely with levodopa than with dopamine agonists?**
A. Dyskinesias
B. Peripheral edema
C. Hallucinations
D. Hypotension

**16. The wife of a man with PD complains that her husband has developed a gambling addiction. Which of the following medications is likely responsible?**
A. Selegiline
B. Entacapone
C. Ropinirole
D. Amantadine

**17. Which medication is useful for reducing dyskinesias in PD but can cause confusion, hallucinations, myoclonus, peripheral edema, and livedo reticularis?**
A. Amantadine
B. Benztropine
C. Rotigotine
D. Selegiline

**18. Trihexyphenidyl has been used for the treatment of PD. What is its mechanism of action?**
A. It is an adenosine receptor antagonist.
B. It is a catechol-*O*-methyltransferase (COMT) inhibitor.
C. It is a monoamine oxidase B (MAO-B) inhibitor.
D. It is a muscarinic antagonist.

**19. What is the mechanism of action of rasagiline?**
A. It is an adenosine receptor antagonist.
B. It is a COMT inhibitor.
C. It is a dopamine agonist.
D. It is a monoamine oxidase B inhibitor.

**20. A patient with PD presents with diarrhea and discolored urine. Which medication is most likely responsible?**
A. Amantadine
B. Apomorphine
C. Entacapone
D. Ropinirole

**21. A patient with PD is unable to obtain his medication from the pharmacy. He develops rigidity, hyperthermia, confusion, tachycardia, and diaphoresis. What is the most likely diagnosis?**
A. Anticholinergic toxicity
B. Dyskinesia–hyperpyrexia syndrome
C. Parkinsonism–hyperpyrexia syndrome
D. Serotonin syndrome

**22. A child is brought to clinic because of frequent startling. The family reports the child was stiff at birth and becomes stiff after being startled. On examination, the child has an exaggerated head retraction reflex. The patient's father also has a history of increased startle. A defect in which of the following receptors is most likely?**
A. Glycine receptor
B. Glutamate receptor
C. γ-Aminobutyric acid (GABA) B receptor
D. Adenosine receptor

**23. Which of the following proteins is abnormal in Parkinson disease 1 (PARK1) and Parkinson disease 4 (PARK4)?**
A. α-Synuclein
B. Glucocerebrosidase
C. Leucine-rich repeat serine/threonine protein kinase 2
D. Parkin
E. Serine/threonine protein kinase

**24. Which of the following is *least* likely to be associated with PD?**
A. Anosmia
B. Depression
C. Oculogyric crisis
D. Rapid eye movement (REM) sleep behavior disorder

**25. Which of the following is a meperidine derivative that can cause symptoms similar to those of PD?**
A. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)
B. Normeperidine
C. Dynorphin
D. Diphenoxylate

**26. A welder presents with personality change and tremor. On examination, he has dystonia and an abnormal gait. He walks on his toes with his spine erect and his elbows flexed. Magnetic resonance imaging (MRI) shows increased signal in the pallidum on T1-weighted images. What is the most likely etiology?**

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A. PD
B. Manganese toxicity
C. Mercury exposure
D. Neurodegeneration with brain iron accumulation

**27. A 59-year-old man presents with falls. He also has had erectile dysfunction. On examination, he has orthostatic hypotension. He also has antecollis and a shuffling gait. He reports that he was given levodopa by another neurologist but it did not work. Which MRI finding is the most likely?**
A. "Mickey Mouse" appearance of the midbrain
B. Midbrain atrophy
C. Midcallosal atrophy
D. Hypointense putamen on T2-weighted scans

**28. Which of the following is the most specific pathologic marker of multiple system atrophy (MSA)?**
A. Glial cytoplasmic inclusions (GCIs)
B. Globose neurofibrillary tangles (NFTs)
C. Loss of cells in the basal nucleus of Meynert
D. Neocortical ballooned neurons

**29. A 60-year-old man presents with difficulties swallowing and falls. On examination, he has a wide-eyed stare, decreased down-gaze, rigidity, and retropulsion. Which of the following genes has been associated with this condition?**
A. *ATM*
B. *HTT*
C. *PARK7*
D. *MAPT*

**30. Which of the following conditions is *least* likely to cause significant autonomic dysfunction?**
A. Dementia with Lewy bodies (DLB)
B. Parkinson disease (PD)
C. Progressive supranuclear palsy (PSP)
D. Spinocerebellar ataxia type 2 (SCA2)

**31. A 60-year-old man is brought to the clinic by his wife because of cognitive problems and because he is not using his left arm. She says he does not seem to know that it is his. He has mild rigidity, decreased sensation, and brisk reflexes in the arm. He also has an upgoing toe on the left. Which of the following is the abnormal protein?**
A. Tau
B. α-Synuclein
C. Amyloid
D. TDP-43

**32. Which of the following is an infectious cause of parkinsonism that is associated with supranuclear ophthalmoplegia and oculomasticatory myorhythmia?**
A. HIV
B. Saint Louis encephalitis
C. West Nile virus
D. Whipple disease

**33. A 70-year-old man presents with cognitive decline. The family reports urinary incontinence. On examination, his gait is slow. His feet have the appearance of being fixed to the ground. He does not have a tremor. MRI of the brain shows enlarged ventricles. Which of the following is most likely to yield the diagnosis?**
A. Check for mutations in the gene *HTT*
B. Large-volume lumbar puncture
C. A trial of carbidopa–levodopa
D. A trial of pramipexole

**34. A 38-year-old man is brought to the office by his wife. She complains that he has been depressed, clumsy, and fidgety. On examination, his saccades are slowed, and he has brisk reflexes including ankle clonus. MRI shows caudate atrophy.**

**a. Which of the following diseases does *not* have the same triplet-repeat gene sequence found in this patient?**
A. Dentatorubral–pallidoluysian atrophy (DRPLA)
B. Kennedy disease (bulbospinal muscular atrophy)
C. Spinocerebellar ataxia type 3 (SCA3)
D. Spinocerebellar ataxia type 10 (SCA10)

**b. Which cells are particularly vulnerable to this disease?**
A. Astrocytes
B. Interneurons of the striatum
C. Medium spiny neurons
D. Pyramidal cells

**35. Tetrabenazine has been used to treat chorea in Huntington disease. What is its mechanism of action?**
A. It blocks dopamine receptors.
B. It inhibits acetylcholinesterase.
C. It inhibits monoamine oxidase.
D. It inhibits a vesicle monoamine transporter.

**36. A 14-year-old girl presents with facial tics, clumsiness, difficulty sitting still, and recent obsessive–compulsive behaviors. She has a darting tongue and spooning of her fingers. She is taking no medications. She was prescribed penicillin for a streptococcal throat infection 2 months ago but took only a few pills. What type of condition is causing her movements?**
A. Autoimmune
B. Genetic
C. Metabolic
D. Trauma

**37. Which of the following medications is *least* likely to cause chorea?**
A. Lithium
B. Oral contraceptives
C. Reserpine
D. Methylphenidate

**38. A 20-year-old otherwise healthy man presents with bilateral hand tremor. He notices it more with movement than at rest. His mother has head and hand tremor. She reports that her tremor improves after a glass of wine. Which treatment should be prescribed?**

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A. Botulinum toxin A injection
B. Clonazepam
C. Propranolol
D. Levetiracetam

**39. Which movement disorder is associated with a wing-beating tremor, risus sardonicus, sunflower cataracts, and increased signal on T2-weighted MRI in the basal ganglia?**

A. Dentatorubral-pallidoluysian atrophy
B. Fahr syndrome
C. Rapid-onset dystonia–parkinsonism
D. Wilson disease

**40. Which of the following proteins is abnormal in the most common form of genetic dystonia?**

A. Epsilon-sarcoglycan
B. Myofibrillogenesis regulator 1
C. TATA-binding protein-associated factor-1 (TAF1)
D. TorsinA

**41. Which of the following statements about dystonia is *false*?**

A. Dystonia is random and unpredictable.
B. Dystonia can improve with a sensory trick.
C. Dystonia can improve at a "null point."
D. Mitochondrial dysfunction can cause dystonia.
E. Botulinum toxin is a treatment for focal and segmental dystonia.

**42. What is the mechanism of action of onabotulinumtoxinA (Botox)?**

A. It inactivates synaptosomal-associated protein 25 (SNAP-25).
B. It inactivates vesicle-associated membrane protein (VAMP).
C. It inactivates syntaxin-1.
D. It is a glycine agonist.

**43. Patients with severe primary dystonia that does not respond to treatment with medications may respond to deep brain stimulation (DBS) of which of the following areas?**

A. Globus pallidus interna
B. Subthalamic nucleus
C. Thalamus
D. Globus pallidus externa

**44. Which of the following conditions is most likely to be responsive to alcohol?**

A. Early onset generalized torsion dystonia (DYT1 or DYT-*TOR1A*)
B. Myoclonus–dystonia (DYT11 or DYT-*SGCE*)
C. Orthostatic myoclonus
D. Rapid-onset dystonia–parkinsonism (RDP)

**45. Which of the following medications is *least* likely to cause myoclonus?**

A. Bismuth (Pepto-Bismol)
B. Gabapentin
C. Meperidine
D. Sodium oxybate

**46. A 7-year-old girl presents with a diagnosis of cerebral palsy. Her main complaint is difficulty walking. She has abnormal leg posturing when she walks in the evening. A medication trial leads to significant improvement. Which medication was used?**

A. Baclofen
B. Edrophonium
C. Carbamazepine
D. Levodopa–carbidopa

**47. A 20-year-old man presents with difficulty moving his neck, which is in an unusual posture. He denies trauma. His medical history is remarkable for gastroesophageal reflux disease, for which he recently started taking metoclopramide. What is the best treatment?**

A. Amantadine
B. Botulinum toxin
C. Diphenhydramine
D. Risperidone

**48. A 5-year-old boy presents with an abnormal gait and falling grades. On examination, he has dystonia, spasticity, and hyperreflexia. MRI shows decreased signal in the globus pallidus except in the anteromedial portion, which has increased signal. Which of the following findings is expected in this condition?**

A. Iron deposition in the basal ganglia
B. Golden ring in Descemet's layer of the cornea
C. A cherry-red spot
D. Deafness

**49. Which autosomal dominant familial ataxia demonstrates an anticipation pattern of inheritance and is associated with seizures and blindness?**

A. SCA3
B. SCA5
C. SCA6
D. SCA7

**50. Which type of spinocerebellar ataxia is associated with anticipation but is *not* caused by a repeat expansion mutation?**

A. SCA1
B. SCA3
C. SCA5
D. SCA7

**51. Which of the following conditions can cause recurrent attacks of ataxia?**

A. Argininosuccinate synthase deficiency
B. Glucose transporter type 1 deficiency
C. Hartnup disease
D. All of the above

**52. Which of the following conditions is most likely to be associated with myokymia?**

A. Episodic ataxia type 1
B. Episodic ataxia type 2
C. Paroxysmal kinesigenic dyskinesia (PKD)
D. Paroxysmal nonkinesigenic dyskinesia

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**53. Mutations in the calcium channel are most likely to cause which of the following conditions?**

A. Episodic ataxia type 1
B. Episodic ataxia type 2
C. Paroxysmal kinesigenic dyskinesia
D. Paroxysmal non-kinesigenic dyskinesia

**54. A 50-year-old man presents with unsteadiness. On examination, he has ataxia and intention tremor. The patient's MRI shows T2 hyperintensities in the middle cerebellar peduncles. The patient's daughter had difficulties in school, and his grandson has intellectual disability and autism. What is the cause of this patient's ataxia?**

A. Dentatorubral-pallidoluysian atrophy
B. Fragile X tremor–ataxia syndrome (FXTAS)
C. Friedreich ataxia
D. Spinocerebellar ataxia type 2

**55. A mother brings her infant to the clinic for brief episodes of weakness involving either side of the body. These are triggered by fatigue, baths, or heat. They last for 1 hour unless the patient naps, in which case they resolve during sleep. What is the most likely diagnosis?**

A. Alternating hemiplegia of childhood (AHC)
B. Basilar migraine
C. Periodic paralysis
D. Todd's paralysis

**56. A 14-year-old boy plays a long soccer game and then indulges in a large pasta meal. The following morning, he has difficulty moving. What is the most likely diagnosis?**

A. Glycogen storage disease type V
B. Mitochondrial neurogastrointestinal encephalopathy (MNGIE)
C. Periodic paralysis
D. Stiff-person syndrome

**57. A 28-year-old pregnant woman reports discomfort in her legs, especially in the evenings. She has difficulty describing the feeling but she says it improves when she shakes her legs or paces. The physical examination is remarkable for mild pedal edema. What is the most likely diagnosis?**

A. Peripheral neuropathy
B. Restless leg syndrome (RLS)
C. Discomfort due to pedal edema
D. Preeclampsia

**58. A 40-year-old woman presents with uncontrolled throwing-like movements in her right arm. What is the most likely site of her lesion?**

A. Caudate
B. Putamen
C. Subthalamic nucleus
D. Globus pallidus external segment

**59. A 5-year-old boy has frequent dystonic posturing of the arm. It typically occurs when he gets up from his chair at school. He remains alert, and the events last less than 1 minute. A mutation in which of the following genes is most likely responsible?**

A. *MR-1*
B. *NKX2.1*
C. *PRRT2*
D. *SLC2A1*
E. *ADCY5*

**60. Deep brain stimulation of which of the following structures is most likely to be used to treat PD that is refractory to medication?**

A. Bilateral caudate
B. Bilateral globus pallidus externa
C. Bilateral putamen
D. Bilateral subthalamic nucleus

**61. A 40-year-old woman presents with worsening muscle cramps, leg stiffness, and falls. Loud noises trigger severe leg cramps, which sometimes cause her to fall. On examination, she has muscle rigidity and lumbar hyperlordosis. Which of the following antibodies are associated with this condition?**

A. Antibodies to glutamic acid decarboxylase 65 (GAD 65)
B. Antibodies to collapsin response mediator protein 5 (CRMP-5)
C. Antibodies to the metabotropic glutamate receptor 5 (mGluR5)
D. Purkinje cell antibody-1 (PCA-1)

**62. Which of the following medications is *least* likely to cause tardive dyskinesia?**

A. Pimozide
B. Risperidone
C. Tetrabenazine
D. Ziprasidone

**63. A mother brings her 15-month-old son to the clinic because of unusual eye movements. She says that his eyes are "jumping all over the place." On examination, sudden arm jerks are also noted. What is the most appropriate next step?**

A. Reassure the mother that these are temporary symptoms caused by a virus.
B. Perform computed tomography (CT) of the chest, abdomen, and pelvis.
C. Refer the patient to ophthalmology.
D. Echocardiogram

**64. Which of the following is most likely to occur in cerebral palsy?**

A. Oculogyric crisis
B. Eye–head gaze saccades
C. Fluctuating symptoms with fasting
D. Onset of symptoms before age 2 years

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# MOVEMENT DISORDERS

## ANSWERS

**1. A**

The hyperdirect pathway is the cortico-subthalamo-pallidal pathway. Specifically, the hyperdirect pathway is from the cerebral cortex (frontal lobe) to the subthalamic nucleus. The subthalamic nucleus activates the globus pallidus internal segment. It also sends fibers to the globus pallidus externa.

**2. B**

The basal ganglia direct pathway is the cortico-striato-pallidal pathway. In the direct pathway, the striatum sends inhibitory (GABAergic) projections to the globus pallidus internal segment and substantia nigra pars reticularis, which send inhibitory (GABAergic) projections to the thalamus. The result is excitation of the thalamus and, ultimately, the cortex.

**3. A**

The basal ganglia indirect pathway involves the globus pallidus externa and then the subthalamic nucleus. The indirect pathway is also known as the cortico-striato-GPe-subthalamo-GPi pathway. Excitation of the indirect pathway results in inhibition of the thalamus.

Injury to the indirect pathway causes decreased inhibition of the pallidum, which ultimately results in hyperkinetic movements (see Figure 10.1).

**4. D**

This patient has a primary motor stereotypy. Stereotypies are repetitive, purposeless behaviors such as hand flapping or body rocking. Compared to tics, primary motor stereotypies in children tend to present earlier, tend to be more rhythmic, and are less likely to be associated with a premonitory urge. Motor stereotypies that occur in children with developmental conditions such as autism are referred to as secondary motor stereotypies.

**5. A**

Chorea and dystonia occur more during movement than during rest. The other disorders listed tend to occur more during rest than movement.

**6. B**

The term *overflow* is used when an unintentional movement accompanies a voluntary movement.

**7. A**

Resistance to passive movement that is independent of velocity is characteristic of rigidity.

Lesions of the basal ganglia can cause rigidity, whereas spasticity is caused by lesions of the corticospinal tract. Rigidity affects both agonist and antagonist muscles. Spasticity tends to affect flexors more than extensors in the upper extremity and extensors more

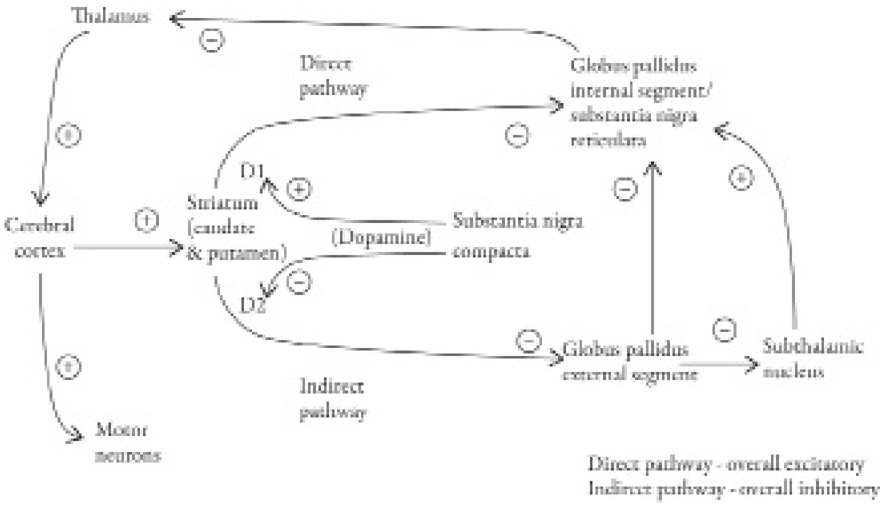
Thalamus
⊖
Direct pathway
Globus pallidus internal segment/ substantia nigra reticulara
⊕
⊖
D1
⊕
Striatum (caudate & putamen)
Cerebral cortex
⊕
Substantia nigra compacta
(Dopamine)
⊖
D2
⊖
⊕
⊖
Globus pallidus external segment
⊖
Subthalamic nucleus
⊕
Indirect pathway
Motor neurons
Direct pathway - overall excitatory
Indirect pathway - overall inhibitory

**Figure 10.1** Direct and indirect pathways: circuitry. SOURCE: From Fisch A. *Neuroanatomy: Draw It to Know It*, 2nd ed., Drawing 18-4. New York: Oxford University Press; 2012.

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than flexors in the lower extremity. Spasticity has a clasp-knife quality. There is increased resistance during early acceleration and then less resistance with continued passive movement. Spasticity is more apparent with fast movement. It is also associated with increased deep tendon reflexes. Rigidity may have a lead pipe or cogwheel quality. Superimposed tremor can cause the cogwheel quality.

Dystonia has qualities similar to rigidity. As in rigidity, resistance is not influenced by speed of passive movement, and rapid reversal of passive movement causes immediate resistance. However, patients with dystonia often have an abnormal posture when awake and improvement during sleep. In addition, performing voluntary movements with the opposite extremity causes a noticeable increase in resistance and abnormal posture of the dystonic extremity.

**8. C**

Tics are rapid, stereotyped, nonrhythmic movements. There is an urge to perform the tic, which is relieved when the tic is performed. Tics can temporarily be suppressed but then may increase after the period of suppression. Tics are suggestible. If the tic is mentioned or demonstrated, the patient may then have the tic. Tics may worsen when patients are hot, under stress, fatigued, bored, or excited. Tics can persist during sleep. Other movement disorders that can continue in sleep include choreoathetosis due to Huntington disease, palatal myoclonus, bruxism, sleep-related leg cramps, sleep-related rhythmic movement disorders, restless leg syndrome, and periodic limb movements.

**9. C**

This patient has Tourette syndrome. ADHD and obsessive–compulsive disorder are common comorbidities. Patients with Tourette syndrome also have an increased incidence of generalized anxiety disorder and depression. Patients should be screened for mood disorders and suicidal thoughts.[1] They may also demonstrate aggression and oppositional behavior and have academic difficulties. Tourette syndrome can be seen in patients with autism spectrum disorder.

**10. B**

Coprolalia (involuntary outburst of socially inappropriate remarks) is not required for the diagnosis of Tourette syndrome.

Patients need to have multiple motor tics and at least one vocal tic to meet criteria. The symptoms must begin before age 18 years; must last at least 1 year; and must not be attributable to a medication, substance, or another medical condition. Tics tend to wax and wane. Tics often improve in adolescence. The Yale Global Tic Severity Scale is a validated measure for assessing tic severity.[1]

**11. B**

Clonidine can be used to treat ADHD, tics, and impulse control problems. Guanfacine is also an option. Both are $\alpha_2$ agonists and can cause drowsiness, bradycardia, and hypotension. Abrupt discontinuation of an $\alpha_2$ agonist can cause rebound hypertension. Guanfacine extended-release can cause prolongation of the QTc interval.[1]

Atomoxetine is helpful for ADHD and would not worsen this patient's tics, but clonidine would treat all of this patient's symptoms. Atomoxetine is useful for treatment of ADHD in patients whose tics have appeared to worsen on stimulants. It is a selective norepinephrine reuptake inhibitor.

Fluphenazine and risperidone would treat this patient's tics, but ADHD and impulse control are a greater concern in this patient. Antipsychotics are associated with a risk for metabolic and extrapyramidal side effects. Some prolong the QT interval.[1]

Behavioral therapy, specifically Comprehensive Behavioral Intervention for Tics (CBIT), is also being used to treat tics.[1]

**12. D**

This patient has Parkinson disease (PD), which causes loss of neurons in the substantia nigra containing melanin. These neurons are immunoreactive with tyrosine hydroxylase, which catalyzes the rate-limiting step in dopamine synthesis. Also, patients with PD have Lewy bodies, which are intraneuronal inclusions that primarily consist of $\alpha$-synuclein.

**13. B**

There are multiple parkinsonian syndromes. Early gait instability raises concern for a parkinsonian syndrome other than idiopathic PD, such as multiple system atrophy (MSA) or progressive supranuclear palsy (PSP). Verbal fluency, particularly lexical fluency, is worse in PSP than in PD.[2]

The tremor of PD is asymmetric. It is a resting tremor; it briefly improves with action. For example, if the arms are outstretched, there is brief improvement, but after a few seconds, the tremor may again be seen. The tremor worsens with mental tasks. (See Boxes 10.1 and 10.2.) Dopamine transporter single-photon emission CT helps differentiate tremor from parkinsonian syndromes from essential tremor but cannot differentiate between various parkinsonian syndromes.

***Box 10.1*** **PARKINSONIAN SYNDROMES**

- Idiopathic Parkinson disease
- Corticobasal degeneration
- Multiple system atrophy
- Progressive supranuclear palsy
- Vascular parkinsonism
- Toxin-induced parkinsonism

**Box 10.2 CHARACTERISTICS OF TREMOR IN PARKINSON DISEASE**

- Asymmetric
- Frequency is 4–6 Hz
- More prominent at rest
- Improves with action
- More prominent during mental tasks, during walking, and with contralateral movement

In addition to symmetric tremor and early gait instability, other red flags that PD is *not* the diagnosis are early dementia, no motor progression for 5 years, absence of nonmotor symptoms, rapid progression, early bulbar involvement, stridor, significant autonomic failure within 5 years of diagnosis, worse anterocollis than expected, and unexpected pyramidal signs.[3]

**14. A**

Carbidopa is an inhibitor of aromatic L-amino acid decarboxylation (AADC), which converts levodopa to dopamine. Carbidopa prevents metabolism of levodopa to dopamine peripherally.

Dopamine is metabolized by monoamine oxidase (MAO) and catechol-*O*-methyltransferase (COMT).

**15. A**

Levodopa is very efficacious at treating bradykinesia and rigidity in PD. However, dyskinesias are more common with levodopa than with dopamine agonists. Sustained-release levodopa does not prevent dyskinesias. Levodopa can also cause hallucinations, nausea, vomiting, orthostatic hypotension, and peripheral edema.

**16. C**

Ropinirole, a dopamine agonist, is most likely responsible. Dopamine agonists can cause disorders of impulse control (e.g., gambling and hypersexuality), sudden sleep attacks, peripheral edema, hallucinations, and hypotension. Dopamine agonists include pramipexole, ropinirole, and rotigotine. Rotigotine is administered as a patch.

Like ropinirole, pramipexole, and rotigotine, apomorphine is a non-ergot dopamine agonist. It can cause sedation and orthostatic hypotension.

**17. A**

Amantadine, which has been used as an antiviral agent, may be helpful in reducing dyskinesias in patients with PD with motor fluctuations. It can cause confusion, hallucinations, myoclonus, peripheral edema, and livedo reticularis.

**18. D**

Trihexyphenidyl is an anticholinergic medication. Specifically, it is a muscarinic antagonist. Anticholinergic medications can cause multiple side effects in the elderly, so trihexyphenidyl is more commonly used in younger patients. It is more helpful for tremor than for the other symptoms of PD.

Benztropine is also anticholinergic.

Anticholinergic medications can cause confusion, hallucinations, blurred vision, dry mouth, constipation, and urinary retention.

**19. D**

Dopamine is metabolized by MAO and COMT. Rasagiline and selegiline are MAO-B inhibitors. They can reduce the off time. Selegiline, but not rasagiline, has an amphetamine metabolite that can cause hallucinations and sleep disturbance.

**20. C**

This patient most likely is taking entacapone. Entacapone and tolcapone are COMT inhibitors that prevent dopamine metabolism and therefore prolong its action. Both can cause diarrhea and discolored urine. Tolcapone has a risk of fatal fulminant liver failure. Opicapone is also a COMT inhibitor.

If a COMT inhibitor is added to levodopa, the dose of levodopa may need to be reduced. COMT inhibitors potentiate levodopa (including its side effects).

**21. C**

This patient has parkinsonism–hyperpyrexia syndrome due to withdrawal of dopaminergic medication. Illness, trauma, surgery, and other stressors can also be triggers.

Anticholinergic toxicity can cause confusion, tachycardia, and hyperthermia; however, in anticholinergic poisoning, the skin is dry and flushed, rigidity is not typical, and bowel sounds are often absent.

Dyskinesia–hyperpyrexia syndrome is a hyperkinetic movement disorder emergency that can occur in patients with PD. It can occur with excessive dopaminergic activity. It is characterized by continuous dyskinetic movements, fever, and altered mental status and can progress to rhabdomyolysis.

Serotonin syndrome can cause agitation, hyperthermia, tachycardia, and diaphoresis. Clues that a patient might have serotonin syndrome are hyperkinetic movement disorders (e.g., tremor and myoclonus), hyperreflexia, mydriasis, and diarrhea. Patients with PD are at risk for serotonin syndrome if they take a combination of medications that increase serotonin, such as MAO inhibitors, selective serotonin reuptake inhibitors, tricyclic antidepressants, and opiates.[4]

**22. A**

This child has hereditary hyperekplexia, which is most often caused by a mutation in the gene encoding the glycine receptor. Clonazepam has been used for treatment.

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**23. A**

Mutations in the gene *SCNA*, which encodes for α-synuclein, are responsible for PARK1 and PARK4. α-Synuclein is found in Lewy bodies.

PARK1, PARK8, and PARK17 are autosomal dominant forms of PD. PARK8 is caused by mutations in the gene *LRRK2*, which encodes for leucine-rich repeat serine/threonine-protein kinase 2. *LRRK2* is a common cause of monogenic PD.[2]

PARK2 is autosomal recessive. It is caused by mutations in the *PARK2* gene, which encodes for parkin. Parkin is a ubiquitin ligase. Mutations in *PARK2* cause early onset PD.

Serine/threonine protein kinase is the abnormal protein in PARK6, which is caused by mutations in *PINK1*. Mutations in *PINK1* also cause early onset, autosomal recessive PD.

Mutations in *GBA*, which encodes glucocerebrosidase, are the most common genetic risk factor for PD. Mutations in *GBA* also can cause Gaucher disease, and patients with type 1 (adult) Gaucher disease can develop parkinsonism. Patients with PD due to *GBA* mutations tend to present earlier, progress faster, and have more cognitive symptoms than patients with sporadic PD.[5]

**24. C**

Oculogyric crisis is an exclusion criterion for PD. It can be seen in postencephalitic parkinsonism. It also is a type of dystonic reaction that occurs with neuroleptic use. In addition, it can be seen in aromatic l-amino acid decarboxylase (AADC) deficiency and in Wilson disease.

Other exclusion criteria for PD are poor response to levodopa, cerebellar signs, a stepwise progression of symptoms, early cognitive problems, early autonomic symptoms, pyramidal signs, and supranuclear palsy. Other red flags that PD is not the diagnosis are cortical sensory loss, early bulbar dysfunction, stridor, and early gait instability.[3]

**25. A**

MPTP can cause symptoms similar to those of PD.

Normeperidine is a derivative of meperidine. It is proconvulsant and can cause seizures.

Dynorphins are endogenous opioid peptides.

Diphenoxylate is a synthetic opioid.

**26. B**

This patient has manganese toxicity, which is a risk for welders. Manganese toxicity causes parkinsonism. It is associated with a "cock-walk" gait.

**27. D**

This is MSA parkinsonism associated with autonomic dysfunction. Autonomic dysfunction precedes motor dysfunction. MRI shows hypointense putamen on T2-weighted scans. Iron deposition can occur in the putamen, which may atrophy.

In the cerebellar form of MSA, a "hot cross bun" sign may be seen. The pontocerebellar fibers in the pons atrophy and have increased signal. Atrophy of the cerebellum and pons is also seen.

MSA is associated with iris atrophy, stridor, myoclonus, and early antecollis and gait instability. REM sleep behavior disorder may precede motor symptoms of MSA.

Midcallosal atrophy occurs in corticobasal degeneration (CBD).

Midbrain atrophy and a Mickey Mouse appearance of the midbrain are seen in PSP.

**28. A**

Glial cytoplasmic inclusions (GCIs), which are characteristic of MSA, have α-synuclein immunoreactivity. α-Synuclein is also found in Lewy bodies. MSA, PD, and dementia with Lewy bodies are synucleinopathies. REM sleep behavior disorder is associated with synucleinopathies and may precede other symptoms.

Globose NFTs are seen in PSP.

Loss of cells in the basal nucleus of Meynert is seen in Alzheimer disease.

Neocortical ballooned neurons are found in CBD.

**29. D**

This patient has PSP, which can be caused by mutations in *MAPT* on 17q21. *MAPT* encodes tau. Features of PSP include a wide-eyed stare, postural instability, and retropulsion. Square wave jerks and slowing of vertical saccades may precede supranuclear vertical gaze palsy. Other characteristic findings in patients with PSP include an angry or puzzled facial expression, early dysphagia, "growling" speech, and a "gunslinger gait" (broad-based with abducted arms that are flexed at the elbows).[6] Frontotemporal dementia can occur in some patients. Midbrain atrophy is seen on MRI in patients with PSP. This causes a hummingbird sign on sagittal images and the Mickey Mouse or morning glory sign on axial images of the midbrain. PSP is a tauopathy (mostly four-repeat [4R] tau). In patients with PSP, tau is found in multiple areas of the brain, including the midbrain, basal ganglia, and prefrontal cortex.[6,7] Tau-immunoreactive astrocytic tufts and oligodendrocytic coils are characteristic of PSP. NFTs can also be seen in patients with PSP. (NFTs are also seen in Alzheimer disease, which is a 3R/4R tauopathy, but the locations of NFTs are different in PSP and Alzheimer disease. In Alzheimer disease, there is greater involvement of neurons in the hippocampal formation and insular cortex.[8,9])

Mutations in the gene *ATM* cause ataxia–telangiectasia.

*PARK7* encodes DJ-1.

*HTT* is discussed later.

**30. C**

Of the conditions listed, PSP is the least likely to cause significant autonomic dysfunction.

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MSA, dementia with Lewy bodies, and SCA2 can cause autonomic dysfunction and parkinsonism.

## 31. A

This patient has CBD, which is a neurodegenerative disease, specifically a tauopathy. Patients with CBD have limb rigidity, akinesia, dystonia, or myoclonus; alien limb phenomenon; and cortical sensory loss. Limb apraxia or mirror movements may be present. MRI shows midcallosal atrophy and asymmetric atrophy of the parietal cortex. Pathology shows achromatic neurons, ballooned neurons, and astrocytic plaques containing accumulated tau. Similar to PSP, 4R tau is found in patients with CBD.[7,8]

In addition to PSP and CBD, other tauopathies are Alzheimer disease (3R/4R tauopathy), chronic traumatic encephalopathy, and frontotemporal dementia.

## 32. D

Whipple disease is caused by the bacterium *Tropheryma whipplei*. Whipple disease tends to affect middle-aged men. In addition to systemic manifestations such as diarrhea, fever, and polyarthritis, Whipple disease can cause neurologic conditions such as dementia, supranuclear ocular palsy, parkinsonism, and oculomasticatory myorhythmia. Intestinal biopsy aids in the diagnosis; periodic acid–Schiff-positive bacteria are seen within macrophages. The treatment is antibiotics.

## 33. B

This patient has normal pressure hydrocephalus (NPH). NPH is a potentially treatable cause of parkinsonism. It is characterized by the triad of dementia, gait disturbance, and urinary incontinence. All three conditions may not be present. Gait impairment is typically present and is often the first sign. The gait is described as a magnetic gait. A large-volume lumbar puncture aids in the diagnosis. Patients with NPH may have improved gait after the lumbar puncture.

## 34a. D and 34b. C

This patient has Huntington disease, which is caused by an increase in the number of CAG repeats in the *HTT* gene. This results in an abnormally long polyglutamine (polyQ) sequence. *HTT*, which is on chromosome 4, encodes the protein huntingtin. Expanded CAG repeats are also found in DRPLA; Kennedy disease (bulbospinal muscular atrophy); and SCA types 1, 2, 3, 6, 7, 12, and 17.

SCA10 is a pentanucleotide repeat disease (ATTCT).

Huntington disease is autosomal dominant. Anticipation occurs. Inheritance from the father is associated with worse prognosis, including earlier onset. Huntington disease causes a subcortical dementia, but changes in mood are seen first. The triad of chorea, dementia, and behavioral changes should raise concern for Huntington disease.[10] Depression, apathy, executive dysfunction, and irritability can occur prior to motor symptoms. Psychomotor slowing is an early indicator of disease progression.[2] Forehead chorea and delayed initiation of saccades may aid in the diagnosis of Huntington disease. Motor impersistence is also seen.[11]

Medium spiny neurons, which are GABAergic, are particularly vulnerable to Huntington disease.

If Huntington disease manifests in childhood (Westphal variant), behavior issues and learning problems may be the earliest signs. Patients with Westphal variant also have bradykinesia, rigidity with or without dystonia, myoclonus, and seizures. Chorea manifests later.

Caudate atrophy occurs in Huntington disease but can also be seen in chorea–acanthocytosis and Huntington disease–like 2, both of which can be associated with chorea, neuropsychiatric conditions, and acanthocytes.

Chorea–acanthocytosis is associated with feeding dystonia, orofacial and orobuccolingual chorea, self-injurious lip and tongue biting, and a “rubber man” gait (truncal instability and sudden trunk spasms).[10,12] Neuropathy, myopathy, and seizures can occur in chorea–acanthocytosis.[10] McLeod syndrome is an X-linked form of chorea–acanthocytosis. It is associated with cardiomyopathy. These patients require autologous blood transfusions to avoid transfusion reactions.[10,12]

Huntington disease–like 2 typically occurs in patients with African ancestry.

## 35. D

Tetrabenazine inhibits vesicle monoamine transporter type 2. This prevents transport of dopamine, serotonin, and norepinephrine into the presynaptic terminal and reduces dopamine transmission. Tetrabenazine can cause depression, suicidality, parkinsonism, and akathisia.

Tetrabenazine is metabolized by the cytochrome P450 enzyme CYP2D6. Patients taking an inhibitor of CYP2D6, such as fluoxetine, should be placed on a smaller dose of tetrabenazine. Tetrabenazine and deutetrabenazine, which is also an inhibitor of vesicular monoamine transporter-2 (VMAT2), have been approved to treat chorea in Huntington disease. (Deutetrabenazine has also been approved to treat tardive dyskinesia, as has valbenazine, which is another VMAT2 inhibitor.[10])

Neuroleptics and clonazepam have been used to treat chorea in Huntington disease. In addition, the glutamatergic-modifying drug amantadine has been used.

## 36. A

This is Sydenham chorea, which is a post-streptococcal autoimmune condition. It is the most common acquired chorea in children.[10] A darting tongue, spooning of the fingers, and milkmaid’s grip are classic signs. The MRI is normal. Sydenham chorea is a consequence of group A β-hemolytic streptococci infection. Elevated antistreptolysin O and anti-DNAse B titers indicate prior infection. Sydenham chorea is a form of rheumatic disease. The patient should be assessed for arthritis and a cardiac murmur and should be treated with penicillin. The chorea can be treated with valproic acid (unless contraindicated) or dopamine receptor antagonists. Benzodiazepines and steroids have also been used in patients with Sydenham chorea. Symptoms may recur during pregnancy (chorea gravidarum).

Chorea can also occur in other autoimmune conditions, such as systemic lupus erythematosus, antiphospholipid antibody syndrome, and Sjögren syndrome.

Chorea can also be a paraneoplastic phenomenon—for example, due to small-cell lung cancer. Other etiologies of chorea are genetic (including metabolic diseases), structural (including hypoxic injury and neoplasms), infectious/parainfectious, medications, metabolic/endocrine/nutritional (e.g., nonketotic hyperglycemia), toxins, vascular, demyelinating, and hematologic.[13]

The most common genetic etiology of chorea in children is benign hereditary chorea (BHC).[12] Huntington disease is the most common genetic chorea in adults. This is followed by C9orf72 disease and spinocerebellar ataxia type 17, which can mimic Huntington diasease.[12]

**37. C**

Multiple medications can cause chorea. Dopaminergic medications, stimulants, and lithium are examples. Antiseizure medications such as carbamazepine, phenytoin, and valproic acid can cause chorea.[10] Oral contraceptives can also cause chorea, as can pregnancy (chorea gravidarum).

Reserpine has been used to treat chorea but has more side effects than some of the other treatment options.

**38. C**

This patient has essential tremor, which is the most common movement disorder. It is autosomal dominant. Essential tremor is bilateral, tends to occur with movement, and improves after alcohol. It can be treated with propranolol or primidone, which have the best evidence. There is less evidence for atenolol, sotalol, gabapentin, and topiramate. There is risk for abuse with clonazepam. Botulinum toxin A injection is reserved for refractory cases. DBS of the ventral intermediate thalamic nucleus has also been used to treat medically refractory limb tremor caused by essential tremor.[14]

**39. D**

Wilson disease causes sunflower cataracts, risus sardonicus, and a wing-beating tremor. Wilson disease, which is also known as hepatolenticular degeneration, results from a defect in copper-transporting adenotriphosphatase (ATPase). Specifically, it is caused by a mutation in the *ATP7B* gene on chromosome 13. Copper excretion from the liver into the bile is impaired, resulting in high levels of copper in the liver. Serum copper and ceruloplasmin are low. Urinary copper is high.

Wilson disease can manifest as liver disease or with neurologic or psychiatric symptoms. It can cause rigidity or movement disorders such as tremor and chorea. A unique finding in Wilson disease is the Kayser–Fleischer ring, which is caused by deposition of copper in Descemet's membrane of the cornea. Sunflower cataracts are less common. Wilson disease is associated with increased signal on T2-weighted MRI in the basal ganglia. In some patients, the face of the giant panda sign can be seen in the midbrain on MRI. Wilson disease is treated with chelation.

Basal ganglia calcification characterizes Fahr syndrome, which can cause parkinsonism and choreoathetosis.

**40. D**

Early onset generalized torsion dystonia (DYT1 or DYT-*TOR1A*) is the most common form of primary genetic dystonia. It is caused by a GAG deletion in the *TOR1A* gene on chromosome 9. This deletion causes an abnormality in the adenosine triphosphate (ATP) binding protein torsinA. Early onset generalized torsion dystonia is autosomal dominant. It begins in a limb, usually in the second decade of life; symptoms then become more generalized.

TATA-binding protein-associated factor-1 (TAF1) is abnormal in dystonia–parkinsonism (DYT3 or DYT/*PARK-TAF1*), which is X-linked.

Myofibrillogenesis regulator 1 is abnormal in paroxysmal nonkinesigenic dyskinesia 1 (DYT8 or DYT-MR-1).

ε-Sarcoglycan is abnormal in myoclonus dystonia (DYT11 or DYT-*SGCE*).

**41. A**

Dystonic movements are patterned and predictable. Dystonia often occurs with initiation of movement or voluntary action, and certain types of dystonia are task-specific (e.g., writer's cramp). Depending on the body region involved, dystonia may have a twisting quality. The presence of a sensory trick (or geste antagoniste) helps diagnose dystonia. Improvement can occur at a "null point." During tasks involving the uninvolved contralateral limb, dystonic posturing may be seen in the involved limb (mirror dystonia). Overflow dystonia refers to involuntary muscle contraction that occurs in addition to the primary site of dystonia. Dystonia worsens with stress and improves when the patient is relaxed or asleep. Dopa-responsive dystonia has a diurnal pattern.

Dystonia may be idiopathic, acquired, or inherited. There are autosomal dominant, autosomal recessive, X-linked, and mitochondrial causes of dystonia.

Chorea is random. If it is rapid, then it can resemble myoclonic jerks.

**42. A**

OnabotulinumtoxinA, or Botox, inactivates SNAP-25.

Some botulinum toxins, such as botulinum toxin B, inactivate vesicle-associated membrane protein (VAMP).

Syntaxin-1 is the target for botulinum toxin C.

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**43. A**

Patients with severe primary dystonia who do not respond to treatment with medications may respond to DBS of the globus pallidus interna.

**44. B**

Myoclonus dystonia (DYT11 or DYT-*SGCE*) is alcohol responsive. (There are other dystonias with myoclonus that do not respond as well to alcohol.)

In patients with DYT11/DYT-*SGCE*, myoclonus usually affects the arms and neck. Dystonia is mild. Myoclonic jerks may occur only during handwriting. DYT11 is caused by mutations in the ε-sarcoglycan gene (*SGCE*) on chromosome 7q. It is autosomal dominant. There is complete paternal penetrance but reduced maternal penetrance due to imprinting.

RDP can be triggered by drinking alcohol. It can also be triggered by infection or other stressors. It is caused by mutations in *ATP1A3*. Mutations in *ATP1A3* also cause alternating hemiplegia of childhood 2 (ACH2), an epileptic encephalopathy, and CAPOS syndrome (cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss).

**45. D**

Sodium oxybate is the least likely to cause myoclonus. It has been used to treat myoclonus but is not a first-line treatment.

**46. D**

This patient has dopa-responsive dystonia. The autosomal dominant form, which is the most common form, is caused by a deficiency of guanosine triphosphate (GTP) cyclohydrolase 1 (GTPCH1); this is also known as DYT/PARK-*GCH1* or DYT5a. The autosomal recessive form is caused by tyrosine hydroxylase deficiency; this is also called DYT/PARK-*TH* or DYT5b. Less common causes of dopa-responsive dystonia are sepiapterin reductase deficiency (DYT/PARK-*SPR*); 6-pyruvoyltetrahydropterin synthase (PTPS) deficiency (DYT/PARK-*PTS*); and quinoid dihydropteridine reductase deficiency (DYT/PARK-*QDPR*).[15] (See Table 10.1.)

*Table 10.1* DOPA-RESPONSIVE DYSTONIAS

| CONDITION | ENZYME AFFECTED |
|---|---|
| **DYT/PARK-*GCH1* or DYT5a*** | **GTP cyclohydrolase 1** |
| **DYT/PARK-*TH* or DYT5b*** | **Tyrosine hydroxylase** |
| **DYT/PARK-*SPR*** | **Sepiapterin reductase** |
| **DYT/PARK-*PTS*** | **6-Pyruvoyltetrahydropterin synthase (PTPS)** |
| **DYT/PARK-*QDPR*** | **Quinoid dihydropteridine reductase (QDPR)** |

*More common causes of dopa-responsive dystonia.

GTPCH1 catalyzes the first step in the synthesis of tetrahydrobiopterin ($BH_4$). $BH_4$ is a cofactor for tyrosine hydroxylase, which converts tyrosine to L-dopa. This is the rate-limiting step in catecholamine synthesis.

(Like GTPCH1, sepiapterin reductase and PTPS are also involved in production of $BH_4$. Quinoid dihydropteridine reductase is involved in regeneration of $BH_4$.)

Botulinum toxin can be helpful for focal or segmental dystonia. Other treatments for dystonia include baclofen, dopamine depleters, benzodiazepines, and anticholinergic medications such as trihexyphenidyl.

Some causes of dystonia are treated with medications related to the pathogenesis of the condition. For example, biotin–thiamine-responsive basal ganglia disease is treated by avoiding triggers and with biotin and thiamine.[16]

**47. C**

This patient has an acute dystonic reaction due to metoclopramide, which is a dopamine $D_2$ receptor blocker. Risperidone is a dopamine $D_2$ receptor antagonist as well, so it should be avoided in this patient. Medications with anticholinergic properties, such as diphenhydramine or benztropine (Cogentin), can be used to treat acute dystonic reaction.

**48. A**

This patient has pantothenate kinase–associated neurodegeneration (PKAN), which is a type of neurodegeneration with brain iron accumulation (NBIA).

NBIA includes multiple disorders characterized by accumulation of iron in the basal ganglia, which results in symptoms such as parkinsonism, dystonia, and choreoathetosis.

PKAN is NBIA type 1, the most common form of NBIA. It is caused by mutations in *PANK2*, which encodes pantothenate kinase. Pantothenate kinase is involved in synthesis of coenzyme A. The classic form of PKAN begins in childhood. An abnormal gait may be the presenting symptom. Patients have rigidity, spasticity, and dystonia. Cognitive changes, seizures, and retinal degeneration may occur. Acanthocytosis may be present. PKAN is associated with the "eye of the tiger" sign, which results from decreased signal on T2-weighted MRI in the globus pallidus and substantia nigra with an area of hyperintensity in the center.

NBIA2B is caused by mutations in the *PLA2G6* gene. Mutations in this gene also cause infantile neuroaxonal dystrophy 1 and PARK14 (adult-onset dystonia–parkinsonism).

NBIA3, also known as neuroferritinopathy, causes adult-onset of chorea, dystonia, parkinsonism, and orolingual dyskinesia.

**49. D**

The spinocerebellar ataxias are autosomal dominant diseases that cause progressive unsteadiness and incoordination with slurred speech.[17] Historically, these have

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been divided into three types of autosomal dominant cerebellar ataxia (ADCA). Spinocerebellar ataxias with prominent extracerebellar abnormalities are classified as ADCA-I. Those with retinal degeneration are ADCA-II. Spinocerebellar ataxias with primarily cerebellar findings are categorized as ADCA-III.

SCA7 is the only disease listed that is in the category ADCA-II. SCA7 causes seizures and retinal degeneration. It demonstrates anticipation.

SCA3 (Machado–Joseph disease) is an autosomal dominant familial ataxia associated with bulged eyes, parkinsonism, facial fasciculations, and eye movement abnormalities. It is caused by mutations in the gene *ATXN3*.

SCA5 and SCA6 are pure cerebellar.

The most common genetic cause of ataxia in patients older than age 40 years is SCA6. One of the earliest signs is positional downbeat nystagmus; when the head is straight back, the patient has downbeat nystagmus.

DRPLA is considered to be one of the ADCAs.

**50. C**

SCA5 demonstrates anticipation but is not caused by a repeat expansion mutation. It is caused by mutations in the gene *SPTBN2*.

Expanded CAG repeats are found in SCA types 1, 2, 3, 6, 7, 12, and 17 and in DRPLA. (In all of these ataxias except for SCA12, the CAG repeats occur in the protein-coding region of the gene and encode polyQ. In SCA12, the repeat is found in the 5′ untranslated region of the gene.)[17]

**51. D**

Some metabolic causes of recurrent ataxia include glucose transporter type 1 (GLUT-1) deficiency, Hartnup disease, maple syrup urine disease, ornithine transcarbamylase deficiency, argininosuccinate synthase deficiency, and pyruvate dehydrogenase deficiency.

**52. A**

Episodic ataxia type 1 (EA1) is the most likely to be associated with myokymia. This is seen between attacks, which are characterized by dysarthria and incoordination and last for minutes. EA1 is treated with carbonic anhydrase inhibitors, such as acetazolamide.

**53. B**

Episodic ataxia type 2 (EA2) is caused by a mutation in the calcium channel. Attacks last hours to days. Between episodes of ataxia, patients have gaze-evoked nystagmus. EA2 is treated with acetazolamide. Caffeine, phenytoin, alcohol, exercise, and stress can trigger events. Some patients have an increased number of CAG repeats in the *CACNA1A* gene. This gene is also associated with SCA6 and with familial hemiplegic migraine.

EA1 is usually caused by a mutation in the potassium channel.

(PKD and PNKD are discussed later.)

**54. B**

This patient has FXTAS. His grandson has fragile X syndrome.

FXTAS tends to affect men older than age 50 years. It causes ataxia and tremor. Parkinsonism, peripheral neuropathy, and psychiatric symptoms can occur. Increased signal is seen in the middle cerebellar peduncles on T2-weighted MRI. It can also be seen in the splenium of the corpus callosum and in the white matter. FXTAS is caused by a premutation in *FMR1*. Patients with FXTAS have an expanded number of CGG repeats but not a sufficient number to cause fragile X syndrome. Females carrying a premutation allele are at risk for fragile X-associated primary ovarian insufficiency.

Dentatorubral–pallidoluysian atrophy causes ataxia, choreoathetosis, and dementia. It is caused by mutations in the gene *ATN1*.

Friedreich ataxia is caused by an expanded GAA trinucleotide repeat in the *FXN* gene on chromosome 9q. It is autosomal recessive.

SCA2 is caused by mutations in *ATN2*.

**55. A**

This patient has alternating hemiplegia of childhood (AHC).

AHC1 is caused by a mutation in the sodium/potassium ATPase, $\alpha_2$ polypeptide (*ATP1A2*) gene on chromosome 1q. Mutations in the gene also cause familial basilar migraine and familial hemiplegic migraine 2.

AHC2 is caused by mutation in the sodium/potassium-transporting ATPase subunit $\alpha_3$ (*ATP1A3*) gene on chromosome 19q. Mutations in the *ATP1A3* gene can also cause dystonia 12 (DYT12 or DYT/PARK-*ATP1A3*), which is rapid-onset dystonia-parkinsonism.

**56. C**

This patient has hypokalemic periodic paralysis.

The periodic paralyses are hereditary channelopathies characterized by flaccid weakness, often resulting from abnormal potassium levels. Carbonic anhydrase inhibitors, such as acetazolamide, may decrease attacks.

A carbohydrate-rich meal and rest after vigorous exercise are triggers for hypokalemic periodic paralysis. Hypokalemic periodic paralysis is caused by a mutation in *CACNA1S* (a calcium channel gene) or in *SCN4A* (a sodium channel gene). Potassium is low during the attacks. Creatine kinase may be elevated.

Similar to hypokalemic periodic paralysis, hyperkalemic periodic paralysis can be caused by mutations in the *SCN4A* gene and can be triggered by rest after exercise; however, potassium tends to be elevated during the attacks. Fasting and potassium-rich foods are also triggers for hyperkalemic periodic paralysis. Some patients have myotonia or paramyotonia.

In addition to causing hypokalemic periodic paralysis and hyperkalemic periodic paralysis, mutations in the

*SCN4A* gene on chromosome 17q also cause paramyotonia congenita, acetazolamide-responsive myotonia congenita, and a congenital myasthenic syndrome.

Mutations in the *KCNJ2* gene, which encodes a potassium inward rectifier, cause Anderson–Tawil syndrome, which is also associated with periods of flaccid weakness triggered by fluctuating potassium levels. These patients also have a prolonged QT interval, ventricular arrhythmias, syndactyly, and characteristic facial features.

Thyrotoxic periodic paralysis is caused by mutations in the *KCNJ18* gene, which also encodes a potassium channel rectifier. Weakness is triggered by thyrotoxicosis and hypokalemia. Glucose should be avoided. A low-carbohydrate diet is recommended.

There is concern about malignant hyperthermia in patients with channelopathies, so depolarizing anesthetic agents should be avoided if the patient undergoes surgery.

Glycogen storage disease type V (GSD-V), or McArdle disease, is the most common carbohydrate metabolism disorder. It is caused by defects in the gene that encodes myophosphorylase, which helps break down glycogen. GSD-V causes exercise intolerance (e.g., muscle cramps and myoglobinuria). Patients do have a second-wind phenomenon. Warming up before exercise and consuming a carbohydrate-rich diet may improve exercise tolerance.

Mitochondrial neurogastrointestinal encephalopathy (MNGIE) results in intolerance of large meals due to gastrointestinal dysmotility. Patients also have cachexia, leukoencephalopathy, weakness, ptosis, external ophthalmoplegia, and a sensorimotor polyneuropathy. Patients with MNGIE have mutations in *TYMP* that result in reduced thymidine phosphorylase levels and elevated levels of thymidine and deoxyuridine in the plasma. Muscle biopsy shows ragged red fibers.[18,19]

**57. B**

This patient has restless leg syndrome (RLS). Pregnancy is a risk factor for RLS. Iron deficiency can contribute to RLS. A ferritin level should also be checked.

**58. C**

This patient has hemiballism, which is caused by lesions of the subthalamic nucleus.

Hemichorea can also occur with lesions of the subthalamic nucleus; however, it has multiple other possible etiologies, including systemic disorders such as nonketotic hyperglycemia, polycythemia vera, and Sydenham chorea.[12]

**59. C**

This patient has paroxysmal kinesigenic dyskinesia (PKD). Patients with PKD have brief, frequent events triggered by movement. The events can occur multiple times per day. PKD is more common in males than in females, and it manifests in the first or second decade of life. Some cases of PKD are caused by mutations in proline-rich transmembrane protein 2 (*PRRT2*) on chromosome 16. PKD may improve with anti-seizure medications such as carbamazepine or phenytoin. Some patients with PKD due to *PRRT2* have self-limited (familial) infantile epilepsy. The combination of convulsions and PKD has been referred to as infantile convulsions and choreoathetosis.

Events are much less frequent in paroxysmal nonkinesigenic dyskinesia (PNKD), but they tend to last longer (minutes to hours). Triggers are alcohol, excitement, and caffeine. PNKD can be seen with mutations in the myofibrillogenesis regulator-1 gene (*MR-1*). PNKD is treated with benzodiazepines, but it does not respond to treatment as well as PKD.

Paroxysmal exercise/exertion-induced dyskinesia (PED) is triggered by prolonged exercise or hyperventilation. Acetazolamide and benzodiazepines have been used for treatment. Some patients with PED have mutations in *SLC2A1*, which causes GLUT-1 deficiency syndrome. These patients may respond to the ketogenic diet. Triheptanoin has also been used.[16]

Mutations in the NK2 homeobox 1 gene *NKX2.1* (or *TITF1*), which encodes thyroid transcription factor 1, are a common cause of BHC. BHC is characterized by hypotonia, motor delay, and chorea beginning before age 5 years. Hypotonia usually precedes chorea. Some patients with BHC due to mutations in *NKX2.1/TITF1* respond to levodopa. Brain–lung–thyroid disease can occur in patients with BHC due to mutations in *NKX2.1/TITF1*. This condition is associated with malignancy, recurrent respiratory tract infections, and thyroid abnormalities.[10,13]

Adenylyl cyclase 5 (*ADCY5*)-related chorea is associated with hypotonia, developmental delay, facial dyskinesia, and chorea that worsens with sleep deprivation.[10,13]

**60. D**

DBS of the bilateral subthalamic nucleus and DBS of the bilateral globus pallidus interna have been used to treat PD.

The goal of DBS is to improve motor symptoms that do not respond to medication. DBS does not prevent progression of the disease. It is recommended that DBS candidates be levodopa responsive. Indications for DBS include disabling dyskinesias, tremor resistant to medication, and the need for frequent dosing of medication to prevent off time. DBS of the subthalamic nucleus can be associated with mood and impulse control disorders.[20]

Unilateral DBS of the ventral intermediate thalamic nucleus has been used to treat tremor in PD and essential tremor.

**61. A**

This patient has stiff-person syndrome, which is associated with antibodies to glutamic acid decarboxylase (GAD) and with antibodies to amphiphysin. Antibodies to GAD 65 are associated with cerebellar degeneration, seizures, and type 1 diabetes mellitus. Anti-GAD 65 antibodies can be seen with small-cell lung cancer but also can be nonparaneoplastic. Antibodies to amphiphysin can be seen in certain patients with breast and lung cancers.

Breast and ovarian cancers are associated with PCA-1, which is also called anti-Yo. These antibodies cause cerebellar degeneration.

Antibodies to CRMP-5 are seen in patients with lung cancer and thymoma. They can cause a number of clinical syndromes.

Antibodies to the metabotropic glutamate receptor 5 (mGluR5) have been found in some patients with Hodgkin lymphoma and limbic encephalopathy. This is called Ophelia syndrome.

**62. C**

Tardive dyskinesia is caused by long-term use of dopamine receptor ($D_2$) blockers, which include antipsychotics such as pimozide, risperidone, and ziprasidone. Metoclopramide, prochlorperazine (Compazine), and promethazine (Phenergan) are also $D_2$ receptor blockers and can cause tardive dyskinesia.

Of the medications listed, tetrabenazine, which depletes monoamines from the nerve terminals, is the least likely to cause tardive dyskinesia. Deutetrabenazine and valbenazine, which are also VMAT inhibitors, have been approved to treat tardive dyskinesia.[10]

**63. B**

This case is concerning for opsoclonus–myoclonus–ataxia syndrome, which is associated with neuroblastoma in children. Imaging of the chest, abdomen, and pelvis should be performed to look for the tumor. Some patients with neuroblastoma have periorbital ecchymoses (raccoon eyes) resulting from metastasis to the orbit. Heterochromia of the iris can occur with a cervicothoracic neuroblastoma. Urine catecholamines and nuclear medicine scans may aid in the diagnosis.

In adults, opsoclonus–myoclonus–ataxia syndrome can occur in the setting of breast or lung cancer and may be associated with ANNA-2/anti-Ri antibodies.

**64. D**

In cerebral palsy, motor symptoms begin before age 2 years and are nonprogressive. The other symptoms (oculogyric crisis, eye–head gaze saccades, and fluctuating symptoms with fasting) are red flags that cerebral palsy is not the diagnosis. Oculogyric crisis occurs with monoamine neurotransmitter disorders. Paroxysmal eye–head movements (eye–head gaze saccades) and fluctuating symptoms with fasting (ataxia and involuntary movements) are seen in GLUT-1 deficiency syndrome due to mutations in *SLC2A1*.[21]

Other red flags that the patient has a cerebral palsy mimic include lack of risk factors for cerebral palsy, motor regression, prominent ataxia, diurnal variation, a positive family history, sensory loss, hyporeflexia/areflexia, and significant autonomic symptoms. Ataxia and oculomotor apraxia raise concern for ataxia–telangiectasia. Diurnal variation and autonomic symptoms raise concern for monoamine neurotransmitter disorders.[21]

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# 11.

# NEUROANATOMY

## QUESTIONS

### CORTEX

1. **Which area of the cortex has a prominent layer V and contains the giant pyramidal cells of Betz?**
   A. Auditory cortex
   B. Frontal eye fields
   C. Primary motor cortex
   D. Visual cortex

2. **Which neurotransmitter is used by the pyramidal cells of the cerebral cortex?**
   A. Acetylcholine
   B. γ-Aminobutyric acid (GABA)
   C. Glutamate
   D. Glycine

3. **A patient describes a "pins and needles" sensation in his arm at the beginning of his seizures. It is thought that the seizures are arising from primary sensory cortex. Which Brodmann area or areas correspond to this region?**
   A. 3, 1, 2
   B. 6
   C. 22
   D. 44, 45

4. **Bilateral lesions of which area can cause ageusia (lack of taste)?**
   A. Insular cortex
   B. Pars triangularis
   C. Superior temporal gyrus
   D. Inferior temporal gyrus

5. **Stimulation of which area of the cortex in one hemisphere can produce bilateral movement?**
   A. Supplementary motor area
   B. Inferior frontal gyrus
   C. Prefrontal cortex
   D. Cingulate gyrus

6. **Which of the following gyri is primary auditory cortex?**
   A. Angular gyrus
   B. Inferior temporal gyrus
   C. Middle temporal gyrus
   D. Transverse gyrus of Heschl

7. **Which area of the cortex directs the activity of the primary motor cortex, assisting in reaching, grasping, and skilled movements?**
   A. Premotor cortex
   B. Orbitofrontal cortex
   C. Dorsolateral prefrontal cortex
   D. Mesial frontal cortex

8. **Where are the frontal eye fields located?**
   A. Superior frontal gyrus
   B. Middle frontal gyrus
   C. Inferior fontal gyrus
   D. Precentral gyrus

### CONNECTING SYSTEMS

9. **Which of the following structures most directly connects the hippocampi?**
   A. Stria terminalis
   B. Hippocampal commissure
   C. Ventral amygdalofugal pathway
   D. Medial forebrain bundle

10. **Which of the following is the largest commissure?**
   A. Anterior commissure
   B. Corpus callosum
   C. Posterior commissure
   D. Supraoptic commissure

11. **Which of the following structures connects the frontal lobe with the temporal and occipital lobes?**
   A. Cingulum
   B. Inferior longitudinal fasciculus
   C. Superior longitudinal fasciculus
   D. Projection fibers

### LIMBIC SYSTEM

12. **In the Papez circuit, which structure carries information from the hippocampal formation to the mammillary bodies?**
   A. Anterior nucleus of the thalamus
   B. Entorhinal cortex
   C. Fornix
   D. Parahippocampal gyrus

13. **Which of the following is the major input and output relay between vision, auditory, and somatosensory association cortex and the hippocampus?**
   A. Entorhinal cortex
   B. Fornix
   C. Piriform cortex
   D. Periamygdaloid cortex

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**14. Which limbic structure is part of the ventral striatum and is involved in motivation, habits, and rewards?**

A. Amygdala
B. Cingulate gyrus
C. Nucleus accumbens
D. Subthalamic nucleus

## BASAL GANGLIA

**15. Fill in the blank: The main input to the basal ganglia is from the ________________.**

A. Cerebral cortex
B. Superior cerebellar peduncle
C. Inferior cerebellar peduncle
D. Thalamus

**16. Which basal ganglia structures act as input nuclei to the basal ganglia?**

A. Caudate nucleus, putamen, and nucleus accumbens
B. Globus pallidus externa and ventral pallidum
C. Internal segment of the globus pallidus and substantia nigra pars reticulata
D. Substantia nigra pars compacta and ventral tegmental area

**17. Which of the following structures is part of the basal ganglia indirect pathway?**

A. Globus pallidus interna
B. Globus pallidus externa
C. Substantia nigra reticulata
D. Substantia nigra pars compacta

**18. Most of the output from the basal ganglia to the thalamus is to which of these structures?**

A. Medial dorsal, ventral lateral, and ventral anterior nuclei
B. Pulvinar and centromedian nuclei
C. Anterior and reticular nuclei
D. Ventroposteromedial and ventroposterolateral nuclei

**19. Which structure in the basal ganglia serves a motor function, projecting to primary motor cortex via the thalamus?**

A. Caudate
B. Globus pallidus
C. Pedunculopontine area
D. Putamen

**20. Fill in the blank: The portions of the striatum involved with emotion are called the _________________.**

A. Ventral tegmental area
B. Ventral striatum
C. Ansa lenticularis
D. Medial forebrain bundle

**21. A lesion of which structure results in hemiballism?**

A. Globus pallidus internal segment
B. Globus pallidus external segment
C. Subthalamic nucleus
D. Substantia nigra pars compacta

## BRAINSTEM

**22. Match the following lesion sites with their associated clinical findings:**

1) Lateral medulla
2) Medial midbrain
3) Medial medulla
4) Ventral pons

A. Contralateral hemiparesis, ipsilateral cranial nerve III (CN 3) palsy
B. Contralateral hemiparesis, ipsilateral CN 6 palsy
C. Ipsilateral hemiataxia, Horner syndrome, loss of pain and temperature of the ipsilateral face and contralateral body
D. Ipsilateral CN 12 palsy, contralateral hemiparesis

**23. Which of the following lesions is *least* likely to cause a pure motor hemiparesis?**

A. A lesion of the corticospinal tract in the basis pontis
B. A lesion of the anterior limb of the internal capsule
C. A cerebral peduncle lesion
D. A lesion of the medullary pyramid

**24. The "locked-in syndrome" is most likely to occur with bilateral lesions of which area?**

A. Lateral medulla
B. Medial medulla
C. Ventral pons
D. Medial midbrain

**25. Which of the following is most likely to be intact in a patient with locked-in syndrome?**

A. Vertical eye movements and blinking
B. Horizontal eye movements
C. Corticobulbar fibers

**26. Lesions of the medulla can cause which of the following?**

A. Neurogenic pulmonary edema
B. Early satiety
C. Inability to sneeze
D. Ondine's curse
E. All of the above

## THALAMUS

**27. In the Papez circuit, which structure provides input to the anterior nucleus of the thalamus?**

A. Cingulate gyrus
B. Mammillary bodies
C. Entorhinal cortex
D. Dentate nucleus

**28. In the Papez circuit, to which structure does the anterior nucleus of the thalamus project?**

A. Cingulate gyrus
B. Mammillary bodies
C. Entorhinal cortex
D. Dentate nucleus

**29. Which nucleus is most likely to be injured in Wernicke–Korsakoff syndrome?**
A. Anterior nucleus
B. Ventral anterior nucleus
C. Mediodorsal nucleus
D. Pulvinar

**30. Match each thalamic nucleus with its description.**
1) Centromedian nucleus
2) Mediodorsal nucleus
3) Pulvinar
4) Ventral lateral nucleus
5) Lateral geniculate nucleus (LGN)
6) Medial geniculate nucleus (MGN)
7) Reticular nucleus
A. This component of the extrageniculate visual pathway is involved in visual attention.
B. This component of the dentarubrothalamic tract receives input from the substantia nigra, globus pallidus, and cerebellum and projects to the motor cortex.
C. This nucleus is involved in a feedback loop between the cortex and striatum; it receives input from the globus pallidus and premotor cortex and projects to the caudate and putamen.
D. This nucleus receives input from limbic structures and has reciprocal connections with the prefrontal cortex.
E. This nucleus functions as a relay station in the auditory pathway.
F. This nucleus sends information to the visual cortex.
G. This nucleus forms a thin layer around the lateral thalamus.

**31. Which thalamic nucleus is involved in the generation of sleep spindles?**
A. Anterior nucleus
B. Mediodorsal nucleus
C. Pulvinar
D. Reticular nucleus

**32. True or False?**
The thalamus integrates and relays information for all sensory modalities.

**33. Which thalamic nucleus is associated with taste sensation?**
A. Anterior nucleus
B. Centromedian nucleus
C. Ventral posterolateral (VPL) nucleus
D. Ventral posteromedial (VPM) nucleus

## CEREBELLUM

**34. Which region of the cerebellum coordinates movement of the trunk?**
A. Cerebellar hemispheres
B. Paravermis
C. Vermis

**35. Which lobe of the cerebellum is involved in eye movements and has connections with the vestibular system?**
A. Anterior
B. Flocculonodular
C. Posterior

**36. Lesions of which lobe of the cerebellum cause the rostral vermis syndrome, which is characterized by a wide-based stance and gait ataxia?**
A. Anterior
B. Flocculonodular
C. Posterior

**37. Lesions of which structure can cause head and trunk tremor, truncal imbalance, and nystagmus?**
A. Cerebrocerebellum
B. Spinocerebellum
C. Vestibulocerebellum

**38. Which deep cerebellar nucleus is responsible for fine motor dexterity?**
A. Dentate
B. Emboliform
C. Globose
D. Fastigial

**39. Which peduncle carries most of the output from the cerebellum?**
A. Inferior cerebellar peduncle
B. Middle cerebellar peduncle
C. Superior cerebellar peduncle

**40. Which type of cell is the major source of inhibitory output from the cerebellar cortex?**
A. Purkinje cell
B. Stellate cell
C. Basket cell
D. Granule cell

**41. Climbing fibers carry information from which of these structures into the cerebellum?**
A. Inferior olive
B. Reticular formation
C. Trigeminal system
D. Vestibular nuclei

## CRANIAL NERVES

**42. Which of the following statements is *false*?**
A. CN 4 is the smallest cranial nerve.
B. CN 4 is the only cranial nerve that exits the brainstem on the dorsal aspect.
C. CN 4 is the only cranial nerve that decussates.
D. CN 6 has the longest intracranial course.

**43. Which nerve is responsible for the afferent limb of the corneal reflex?**
A. The ophthalmic division of the trigeminal nerve (V1)
B. The maxillary division of the trigeminal nerve (V2)
C. The mandibular division of the trigeminal nerve (V3)
D. Cranial nerve III

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**44. A cavernous sinus thrombosis is least likely to involve which nerve?**

A. The maxillary branch of the trigeminal nerve (V2)
B. The mandibular division of the trigeminal nerve (V3)
C. Cranial nerve IV
D. Cranial nerve VI

**45. Which cranial nerve is responsible for general sensation from the anterior two-thirds of the tongue?**

A. The trigeminal nerve
B. The facial nerve
C. The glossopharyngeal nerve
D. The vagus nerve

## SPINAL CORD

**46. A 55-year-old woman presents with falling and numbness. On examination, she has loss of vibration on the right up to T10 and loss of pain and temperature up to T10 on the left. What other finding would you expect on examination?**

A. Numbness of the right upper extremity
B. Numbness of the left upper extremity
C. Weakness of the right lower extremity
D. Weakness of the left lower extremity

**47. Which of the following are the most lateral tracts of the spinal cord and therefore the most vulnerable to extrinsic lateral insults?**

A. Dorsal and ventral spinocerebellar tracts
B. Lateral corticospinal tract
C. Lateral vestibulospinal tract
D. Tectospinal tract

**48. A patient presents with bilateral leg weakness, decreased pain sensation up to the level of the umbilicus, bowel and urinary incontinence, and intact proprioception and vibration. Which of the following is the most likely diagnosis?**

A. Anterior spinal artery infarct
B. Cauda equina lesion
C. Conus medullaris lesion
D. Poliomyelitis

**49. Which of the following disorders affect the posterior columns and corticospinal tracts of the spinal cord?**

A. Copper deficiency myelopathy after gastric bypass surgery
B. Nitrous oxide myelopathy
C. Vitamin $B_{12}$ deficiency
D. Human T-cell leukemia virus type 1 (HTLV-1)–associated myelopathy
E. All of the above

**50. Which of the following diseases is *least* likely to affect the posterior columns?**

A. AIDS-associated myelopathy
B. Tabes dorsalis
C. Posterior spinal artery infarct
D. Poliomyelitis

**51. A woman presents with bilateral hand weakness. On examination, she has muscle wasting in both hands. She has decreased pinprick and temperature sensation in the arms and shoulders, but light touch, vibration, and proprioception are intact. Reflexes in the arms are decreased. What is her diagnosis?**

A. Syringomyelia
B. Vitamin E deficiency
C. Primary lateral sclerosis
D. Primary muscular atrophy

## SPINAL ROOTS AND PERIPHERAL NERVES

**52. Occipital neuralgia involves which nerve root?**

A. C1
B. C2
C. C3

**53. Which of the following statements is *false*?**

A. C1 has no sensory roots.
B. There is no C8 vertebra.
C. A C5–C6 disc herniation tends to affect the C5 nerve root.
D. Batson's plexus may allow the spread of metastases and infections in the epidural space.

**54. A 60-year-old woman presents with neck and right shoulder pain, weakness of her right hand, and numbness and tingling of her right fourth and fifth digits. She has decreased sensation in the fourth and fifth digits and weakness of the intrinsic hand muscles on the right. Reflexes are normal. Which of the following diagnoses is most likely?**

A. C5 radiculopathy
B. C6 radiculopathy
C. C7 radiculopathy
D. C8 radiculopathy

**55. Which nerve root exits above the T1 vertebral bone?**

A. C6
B. C7
C. C8
D. T1

**56. Which muscle above the knee is supplied by the peroneal division of the sciatic nerve?**

A. Gluteus minimus
B. Small head of the biceps femoris
C. Soleus
D. Gracilis

**57. True or False?**

Weakness of foot inversion suggests that a patient's foot drop is caused by a lesion proximal to the peroneal nerve at the fibular neck.

**58. Which of the following nerves gives rise to the posterior interosseous nerve?**

A. Axillary
B. Medial
C. Radial
D. Ulnar

## CEREBROSPINAL FLUID AND THE VENTRICULAR SYSTEM

**59. What is the rate of cerebrospinal fluid (CSF) production?**

A. 5 mL/hr
B. 10 mL/hr
C. 20 mL/hr
D. 35 mL/hr

**60. Where is CSF absorbed into the blood?**

A. Arachnoid granulations
B. Choroid plexus
C. Foramina of Luschka and Magendie
D. Foramen of Monro

## BLOOD–BRAIN BARRIER

**61. Fill in the blank: The blood–brain barrier results from the presence of _______________ that link capillary endothelial cells in the brain.**

A. Cadherins
B. Connexins
C. Integrins
D. Tight junctions

**62. Fill in the blank: Areas of the brain where the blood–brain barrier is interrupted are called _______________.**

A. Adherens junctions
B. Circumventricular organs
C. Desmosomes
D. Gap junctions

**63. Fill in the blank: The _______________ is also known as the chemotactic trigger zone because it detects toxins that cause vomiting.**

A. Median eminence
B. Area postrema
C. Organum vasculosum of the lamina terminalis
D. Subfornical organ

## HYPOTHALAMUS

**64. Which hypothalamic nucleus is most directly involved in regulating circadian rhythms?**

A. Anterior
B. Arcuate
C. Medial preoptic
D. Suprachiasmatic

**65. Which nucleus of the hypothalamus provides most of the innervation to preganglionic sympathetic neurons in the spinal cord?**

A. Anterior
B. Lateral nucleus
C. Paraventricular
D. Supraoptic

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# NEUROANATOMY

## ANSWERS

### CORTEX

**1. C**

Primary motor cortex (Brodmann area 4) has a prominent layer V and contains the giant pyramidal cells of Betz.

The majority of the cortex is organized into six layers; together, they make up the neocortex. Layer V is called the large pyramidal layer or the internal pyramidal layer. The primary motor cortex has a relatively thicker layer V because of its projections to the brainstem, striatum, and spinal cord. Layers II and III are involved with cortical–cortical connections. Layer IV, the internal granular layer, receives information from the thalamus and is thickest in primary sensory cortices.

**2. C**

The pyramidal cells of the cerebral cortex use glutamate, which is excitatory.

Glycine, which is inhibitory, is predominantly found in the spinal cord.

**3. A**

Primary sensory cortex is Brodmann areas 3, 1, 2. This corresponds to the postcentral gyrus, which receives somatosensory input from the VPL and VPM nuclei of the thalamus.

Brodmann area 6 is premotor cortex and supplementary motor cortex.

Brodmann area 22 is Wernicke's area.

Brodmann areas 44 and 45 are Broca's area.

**4. A**

Bilateral lesions of the insular cortex can cause ageusia.

**5. A**

The supplementary motor area (Brodmann area 6) has its own smaller motor homunculus that is independent from primary motor cortex. Stimulation of the supplementary motor area can produce bilateral movement.

**6. D**

The transverse gyrus of Heschl is primary auditory cortex (Brodmann areas 41 and 42). Unilateral injury to the primary auditory cortex does *not* cause deafness.

**7. A**

The premotor cortex (Brodmann area 6) directs the activity of the primary motor cortex, assisting in reaching, grasping, and skilled movements. It lies anterior to the primary motor cortex (Brodmann area 4) on the lateral surface of the cerebral hemisphere. (The primary motor cortex is on the precentral gyrus.) Like the primary motor cortex, the premotor cortex contains a homunculus.

Orbitofrontal cortex is responsible for social behaviors, conscious perception of smell, and awareness of flavors. Lesions cause disinhibition and socially inappropriate behavior. Lesions can also cause poor olfactory discrimination.

The dorsolateral prefrontal cortex is involved in planning, judgment, problem-solving, and executive function.

The mesial frontal cortex and anterior cingulate gyrus are involved in motivation. Lesions cause abulia and reduced spontaneous movements. Patients may also have urinary incontinence and gait disturbance.

**8. B**

The frontal eye fields are located in the middle frontal gyrus.

### CONNECTING SYSTEMS

**9. B**

The hippocampal commissure joins the hippocampi.

The stria terminalis and ventral amygdalofugal pathway connect the amygdala and hypothalamus.

The medial forebrain bundle connects the septal area and amygdala to the midbrain.

**10. B**

Commissures connect the two hemispheres, allowing information to travel from one hemisphere to the other. The largest commissure is the corpus callosum. Other commissures include the anterior, posterior, hippocampal, habenular, and supraoptic commissures.

**11. C**

The superior longitudinal fasciculus connects the frontal lobe with the temporal and occipital lobes.

Association fibers connect structures within one hemisphere. These fibers tend to arise from pyramidal cells in layers II and III of the cerebral cortex. The cingulum, inferior longitudinal fasciculus, superior longitudinal fasciculus, uncinate fasciculus, and occipitofrontal fasciculus are long association fibers (see Box 11.1).

### *Box 11.1* LONG ASSOCIATION FIBERS

- The uncinate fasciculus connects the inferior frontal lobe with the anterior temporal lobe.
- The cingulum, which is within the cingulate gyrus, connects the anterior perforated substance with the parahippocampal gyrus.
- The superior longitudinal fasciculus connects the frontal lobe with the temporal and occipital lobes.
- The inferior longitudinal fasciculus connects the temporal and occipital lobes.
- The occipitofrontal fasciculus connects the frontal lobe to the temporal and occipital lobes.

Projection fibers connect the cerebral cortex to subcortical structures, the brainstem, and the spinal cord.

U fibers are short association fibers that connect adjacent gyri.

## LIMBIC SYSTEM

**12. C**

In the Papez circuit, the fornix carries information from the hippocampal formation to the mammillary bodies.

**13. A**

Input from vision, auditory, and somatosensory association cortex travels to the hippocampus by way of the entorhinal cortex. Also, olfactory input enters the hippocampus through the entorhinal cortex.

**14. C**

The nucleus accumbens, which is part of the ventral striatum, is involved in motivation, habits, and rewards. Dopamine is a key neurotransmitter in this process.

The amygdala is a limbic structure, but it is not part of the ventral striatum. In the amygdala, emotions are associated with stimuli. The amygdala has connections to the autonomic nervous system. Stimulation of the amygdala can cause fear.

The cingulate gyrus is a limbic structure, but it is not part of the ventral striatum.

The subthalamic nucleus is not a limbic structure.

## BASAL GANGLIA

**15. A**

The main input to the basal ganglia is from the cerebral cortex, mainly the frontal lobe.

**16. A**

The caudate nucleus, putamen, and nucleus accumbens receive input to the basal ganglia.

The internal segment of the globus pallidus, ventral pallidum, and substantia nigra pars reticulata are output nuclei.

The substantia nigra pars compacta and ventral tegmental area are intrinsic nuclei, as are the external segment of the globus pallidus and intrinsic part of the ventral pallidum.

**17. B**

The basal ganglia direct pathway is the cortico-striato-pallidal pathway. In the direct pathway, the striatum sends projections to the globus pallidus internal (GPi) segment and substantia nigra pars reticularis, which sends projections to the thalamus. The end result is excitation of the thalamus and ultimately the cortex.

The basal ganglia indirect pathway involves the globus pallidus externa (GPe) and then the subthalamic nucleus. This pathway is also known as the cortico-striato-GPe-subthalamo-GPi pathway.

**18. A**

Most of the output from the basal ganglia to the thalamus is to the medial dorsal, ventral lateral, and ventral anterior nuclei. The ventral lateral and ventral anterior nuclei send information to the motor cortex, premotor cortex, and supplementary motor area. Information from the medial dorsal nucleus travels to the prefrontal cortex.

**19. B**

The GPi and the substantia nigra are the two major output nuclei of the basal ganglia. Motor information from the GPi travels to the ventral anterior and ventral lateral nuclei of the thalamus and then to the primary motor cortex.

**20. B**

The nucleus accumbens and adjacent portions of the caudate and putamen form the ventral striatum. These structures are involved in emotion.

The ansa lenticularis and the lenticular fasciculus are pathways between the internal segment of the globus pallidus and the thalamus.

Information travels from the ventral tegmental area to the striatum through the median forebrain bundle.

**21. C**

A lesion of the subthalamic nucleus can cause hemiballism.

## BRAINSTEM

**22.**

1) C. Lesions of the lateral medulla cause ipsilateral hemiataxia, Horner syndrome, and loss of pain and temperature of the ipsilateral face and contralateral body.

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2) A. Lesions of the medial midbrain cause contralateral hemiparesis and an ipsilateral CN 3 palsy.
3) D. Lesions of the medial medulla cause an ipsilateral CN 12 palsy and contralateral hemiparesis.
4) B. Lesions of the ventral pons cause a contralateral hemiparesis and an ipsilateral CN 6 palsy.

**23. B**

The corticospinal tract travels in the posterior limb of the internal capsule. A lesion here can cause a pure motor hemiparesis. Similarly, lesions of the corticospinal tract in the midbrain (cerebral peduncle), basis pontis, or medullary period can cause a pure motor hemiparesis.

**24. C**

Bilateral ventral pontine lesions—for instance, those caused by basilar occlusion—are the most likely cause of locked-in syndrome.

**25. A**

Patients with locked-in syndrome have quadriplegia due to bilateral corticospinal tract lesions (secondary to involvement of the basis pontis). They also are unable to speak due to corticobulbar tract involvement and may have impaired horizontal eye movements due to CN 6 lesions. Vertical eye movements are intact, and the patient can blink. Somatosensory and reticular pathways are not affected.

**26. E**

Lesions of the medulla can cause neurogenic pulmonary edema, early satiety, inability to sneeze, and Ondine's curse.

Inability to sneeze is a rare finding in Wallenberg syndrome (lateral medullary syndrome) that is caused by involvement of the descending tract and spinal nucleus of the trigeminal nerve.

Lesions involving the nucleus ambiguus and reticular formation can cause Ondine's curse, the lack of automatic breathing.

## THALAMUS

**27. B**

In the Papez circuit, the mammillary bodies provide input to the anterior nucleus of the thalamus.

**28. A**

The anterior nucleus of the thalamus has input from the mammillary nucleus and projects to the cingulate gyrus in the Papez circuit.

In the Papez circuit, the fornix carries information from the hippocampal formation to the mammillary bodies, and the mammillothalamic tract connects the mammillary bodies and the anterior nucleus of the thalamus. Information then travels to the cingulate gyrus and finally back to the hippocampus via the entorhinal cortex.

**29. C**

The mediodorsal nucleus is the most likely to be injured in Wernicke–Korsakoff syndrome.

**30.**

1) C. The centromedian nucleus is involved in a feedback loop between the cortex and striatum. It receives input from the globus pallidus and premotor cortex and projects to the caudate and putamen.
2) D. The mediodorsal nucleus receives input from limbic structures and has reciprocal connections with the prefrontal cortex.
3) A. The pulvinar, which has reciprocal connections with parietal, temporal, and occipital cortex, is part of the extrageniculate visual pathway and is involved with visual attention.
4) B. The ventral lateral nucleus is a component of the dentarubrothalamic tract; it receives input from the substantia nigra, globus pallidus, and cerebellum and projects to the motor cortex.
5) F. The LGN sends information to the visual cortex.
6) E. The MGN is a relay station in the auditory pathway.
7) G. The reticular nucleus forms a thin layer around the lateral thalamus.

**31. D**

The reticular nucleus is involved in the generation of sleep spindles.

**32. False**

The thalamus integrates and relays information for all sensory modalities except olfaction.

**33. D**

The LGN, MGN, VPL nucleus, and VPM nucleus are thalamic nuclei involved with sensation. The LGN is involved in vision, and the MGN is involved in hearing. The VPL nucleus is involved in limb sensation. The VPM nucleus is involved in taste sensation.

The ventral anterior and ventral lateral nuclei are involved with motor function.

The anterior and mediodorsal nuclei are involved with limbic functions.

## CEREBELLUM

**34. C**

The cerebellum can be divided vertically into the vermis, paravermis, and cerebellar hemispheres.

The vermis coordinates truncal tone and movement.

The paravermis regulates limb movements. The paravermis is located just lateral to the vermis (in the medial cerebellar hemispheres).

The cerebellar hemispheres are involved in ipsilateral fine motor control.

## 35. B

The cerebellum can be divided horizontally into the anterior, posterior, and flocculonodular lobes.

The anterior lobe contains portions of the vermis and paravermis. It receives ipsilateral input from the spinal cord through the spinocerebellar pathways. (The cerebellum has ipsilateral connections with the body and spinal cord and contralateral connections with the cerebrum.)

The posterior lobe receives cerebrocortical information via the pons. The cerebellar hemispheres are in the posterior lobe.

The flocculonodular lobe, which consists of the flocculus and the nodulus (inferior vermis), receives vestibular input (see Table 11.1).

*Table 11.1* CEREBELLAR ANATOMY

| LOBE | ANATOMIC STRUCTURES IN THE LOBE | INPUT TO THE LOBE |
|---|---|---|
| Anterior | Vermis and paravermis | Spinocerebellar |
| Posterior | Cerebellar hemispheres | Cerebrocortical |
| Flocculonodular | Flocculus and nodulus (inferior vermis) | Vestibular |

## 36. A

Patients with alcoholism tend to develop the rostral vermis syndrome, which affects the anterior lobe of the cerebellum. The syndrome is characterized by a wide-based gait and gait ataxia. The anterior lobe of the cerebellum receives the majority of the input from the spinocerebellar tracts.

The caudal vermis syndrome, which results from injury to the flocculonodular lobe, is characterized by truncal ataxia. Medulloblastoma is a cause of caudal vermis syndrome.

Cerebellar hemispheric syndrome is caused by lesions of the posterior lobe and is characterized by ataxia of ipsilateral appendicular movements (see Table 11.2).

*Table 11.2* CEREBELLAR LESIONS

| LOBE | ANATOMIC STRUCTURES IN THE LOBE | SYNDROME CAUSED BY LESION OF THE LOBE |
|---|---|---|
| Anterior | Vermis and paravermis | Rostral vermis syndrome |
| Posterior | Cerebellar hemispheres | Cerebellar hemispheric syndrome |
| Flocculonodular | Flocculus and nodulus (inferior vermis) | Caudal vermis syndrome |

## 37. C

The cerebellum has been divided into the spinocerebellum (also known as the paleocerebellum), the vestibulocerebellum (also known as the archicerebellum), and the cerebrocerebellum (also known as the neocerebellum or pontocerebellum).

The spinocerebellum/paleocerebellum corresponds to the anterior lobe. The vermis and paravermis are part of the spinocerebellum.

The vestibulocerebellum/archicerebellum corresponds to the flocculonodular lobe.

The cerebrocerebellum/neocerebellum corresponds to the posterior lobe. The lateral cerebellar hemispheres are part of the cerebrocerebellum. Due to its connections with the pons, it is also called the pontocerebellum. It is involved in planning and initiating movements and fine motor control.

The name of the vestibulocerebellum is derived from its vestibular connections. The flocculonodular lobe, which is in the vestibulocerebellum, receives information from and sends information to the vestibular nuclei. It is involved in maintaining body equilibrium and controlling eye movements. Lesions cause head and trunk tremor, truncal imbalance, and nystagmus (see Table 11.3).

*Table 11.3* CLINICAL FINDINGS WITH CEREBELLAR LESIONS

| LOBE | INPUT TO THE LOBE | ANATOMIC STRUCTURES IN THE LOBE | EFFECTS OF A LESION OF THE LOBE |
|---|---|---|---|
| Anterior (paleocerebellum, spinocerebellum) | Spinocerebellar tracts | Vermis and paravermis | Wide-based gait, gait ataxia, dysmetria, dysdiadochokinesia, intention tremor |
| Posterior (neocerebellum, cerebrocerebellum, pontocerebellum) | Cerebrocortical | Lateral cerebellar hemispheres | Delayed initiation or termination of movements, abnormal timing of movements, disturbance of skilled movements |
| Flocculonodular (archicerebellum, vestibulocerebellum) | Vestibular | Flocculus and nodulus (inferior vermis) | Head and trunk tremor, truncal imbalance, nystagmus |

**38. A**

The deep cerebellar nuclei of the cerebellum are the dentate, emboliform, globose, and fastigial nuclei.

The dentate nucleus, which is the most lateral of the deep nuclei, receives information from the cerebellar hemispheres and indirectly from the cortex. It sends information to ventral lateral and ventral anterior nuclei of the thalamus and impacts the corticobulbar and corticospinal tracts. It is involved in motor planning and contributes to fine motor dexterity.

The dentate nucleus is part of the Guillain–Mollaret triangle, which is also known as the dentato-rubro-olivary pathway. Lesions in this pathway can cause palatal tremor.

The globose and emboliform nuclei, together known as the interposed nuclei, receive information from the paravermis. They send information to the red nucleus, the origin of the rubrospinal tract, which affects flexor tone.

The fastigial nucleus, which is the most medial of the deep nuclei, receives information from the vermis. It sends information to the reticular and vestibular nuclei and regulates the reticulospinal and vestibulospinal tracts (see Table 11.4).

*Table 11.4* DEEP CEREBELLAR NUCLEI

| NUCLEUS | STRUCTURE PROVIDING INPUT TO THE NUCLEUS | TRACTS REGULATED BY THE NUCLEUS |
|---|---|---|
| **Fastigial** | **Vermis** | **Reticulospinal and vestibulospinal** |
| **Interposed (emboliform and globose)** | **Paravermis** | **Rubrospinal** |
| **Dentate** | **Lateral hemisphere** | **Corticospinal and corticobulbar** |

**39. C**

The superior cerebellar peduncle connects the cerebellum to the midbrain. The middle cerebellar peduncle connects the cerebellum to the pons. The inferior cerebellar peduncle connects the cerebellum to the medulla.

The superior cerebellar peduncle carries most of the output from the cerebellum. It contains fibers from the dentate, emboliform, and globose nuclei. Efferent fibers from the superior peduncle include the dentatorubral tract, the dentatothalamic tract, and the uncinate bundle of Russell.

**40. A**

Purkinje cells inhibit the deep cerebellar nuclei and are the major source of inhibitory output from the cerebellar cortex. Axons of some Purkinje cells project to vestibular nuclei.

**41. A**

Mossy fibers and climbing fibers provide input to the cerebellar cortex.

Climbing fibers travel from the inferior olive to the cerebellum. Climbing fibers, which are excitatory, make multiple synaptic contacts with a single Purkinje cell.

Mossy fibers excite granule cells, which then excite multiple Purkinje cells.

Most types of cells (i.e., Purkinje, stellate, basket, and Golgi cells) in the cerebellar cortex are inhibitory. Granule cells are the exception.

## CRANIAL NERVES

**42. D**

CN 4 (the trochlear nerve) has the longest intracranial course. It is the smallest cranial nerve. It is the only cranial nerve that decussates and the only one that exits the brainstem on the dorsal aspect. CN 4 travels through the cavernous sinus. It exits the skull through the superior orbital fissure.

CN 4 innervates the superior oblique muscle, which is responsible for depression and intorsion of the eye. Trochlear nerve palsy causes hypertropia and extorsion of the affected eye. Acute onset of an isolated CN 4 palsy—for instance, due to trauma—causes vertical diplopia. Patients often try to compensate by tilting the head to the opposite side (to correct extorsion) and tucking the chin (to correct hypertropia).

**43. A**

V1 is the afferent limb of the corneal reflex. CN 7 is the efferent limb. The interneuron is the spinal nucleus of the trigeminal nerve.

The jaw-jerk reflex is mediated by the trigeminal nerve. When the lower jaw is tapped, the masseter and temporalis muscles contract. The 1a motor fibers in the mandibular division of the trigeminal nerve (V3) provide the afferent information. This information travels to the mesencephalic nucleus of the trigeminal nerve. The efferent limb is the mandibular fibers originating in the motor nucleus of the trigeminal nerve.

**44. B**

A cavernous sinus thrombosis is least likely to involve V3, which does not travel in the cavernous sinus.

The cavernous sinus syndrome can affect the abducens, trochlear, and oculomotor nerves as well as the V1 and V2 divisions of the trigeminal nerve (see Figure 11.1).

The abducens, trochlear, and oculomotor nerves and V1 travel through the superior orbital fissure.

**45. A**

The trigeminal nerve is responsible for *general sensation* from the anterior two-thirds of the tongue. The facial nerve is responsible for *taste* from the anterior two-thirds of the tongue.

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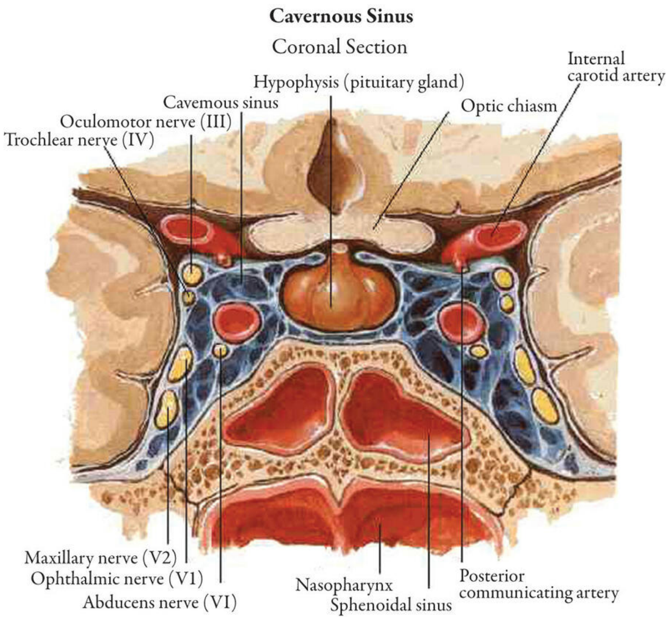

**Figure 11.1** Relationship of cranial nerves within the cavernous sinus. SOURCE: From Sundaram V, Barsam A, Alwitry A, Khaw P. *Training in Ophthalmology,* Fig. 9.5. New York: Oxford University Press; 2009.

The V3 division of the trigeminal nerve gives rise to the mandibular nerve, which exits the skull through the foramen ovale, and innervates the muscles of mastication. A branch of V3 becomes the lingual nerve, which provides tactile sensation to the lower gums and anterior two-thirds of the tongue. V3 also gives rise to mental and inferior dental branches.

Taste sensation from the anterior two-thirds of the tongue travels in the chorda tympani nerve (a branch of the facial nerve) to the geniculate ganglion.

The glossopharyngeal nerve provides taste and tactile sensation for the posterior one-third of the tongue.

The vagus nerve is responsible for taste from the epiglottis and pharynx.

Information about taste travels through the cranial nerves (facial, glossopharyngeal, and vagus) to the rostral solitary nucleus. Then it travels through the central tegmental tract to the VPM nucleus of the thalamus. Next, it travels to the insular cortex, posterior limb of the internal capsule, and operculum (gustatory cortex).

## SPINAL CORD

**46. C**

This is Brown–Séquard syndrome, which results from hemicord lesions. Features of this syndrome include ipsilateral upper motor neuron–type weakness due to involvement of the corticospinal tract; ipsilateral loss of vibration sense and joint position due to involvement of the dorsal columns; and contralateral loss of pain and temperature sensation.

**47. A**

The dorsal and ventral spinocerebellar tracts are lateral within the spinal cord and are vulnerable to extrinsic lateral insults. They carry proprioceptive information from the lower extremities and trunk to the cerebellum.

The dorsal spinocerebellar tract arises from Clarke's nucleus, which extends from C8 to L2 in the spinal cord. It enters the cerebellum through the inferior cerebellar peduncle. It is an uncrossed tract.

The ventral spinocerebellar tract begins in the lumbar and sacral segments of the spinal cord. Most axons cross, but some do not. The tract enters the cerebellum through the superior cerebellar peduncle.

The lateral vestibulospinal tract provides extensor tone.

**48. A**

This patient has an anterior spinal artery infarct, which affects the anterior two-thirds of the cord. The dorsal columns are spared, resulting in intact proprioception and vibration. There are multiple etiologies of anterior spinal artery infarction, one of which is aortic surgery. The anterior spinal artery, which arises from the vertebral arteries, receives blood from radicular arteries. The artery of Adamkiewicz, which is the largest radicular artery in the lower thoracic and upper lumbar region, can be injured during aortic surgery, resulting in anterior spinal artery infarction.

A cauda equina lesion involves the lumbosacral nerve roots below L2, not the spinal cord itself. The lesion causes radicular back pain and bilateral asymmetric leg weakness and sensory loss (all modalities). Later, there may be bladder involvement and impotence.

A conus medullaris lesion causes sensory loss in a saddle distribution. Bowel and bladder are involved early.

(Poliomyelitis is discussed later.)

**49. E**

All of the conditions listed affect the posterior columns and corticospinal tracts, causing a posterolateral column syndrome. Patients have loss of vibration and proprioception, sensory ataxia, and a positive Romberg sign due to posterior column involvement and spastic paralysis due to involvement of the corticospinal tracts.

**50. D**

Poliomyelitis affects the anterior horn cells. It causes asymmetric weakness and muscle atrophy. Sensation is normal.

AIDS-associated myelopathy, tabes dorsalis, and posterior spinal infarcts affect the posterior columns.

**51. A**

This patient has syringomyelia, a cavity in the spinal cord, in the cervical region. A syrinx typically affects crossing spinothalamic fibers first, causing loss of pain and temperature in a cape-like distribution. (Loss of pain and temperature sensation with preservation of light touch, vibration, and proprioception is called dissociated sensory loss.) Anterior horn atrophy can cause weakness and muscle wasting. If the descending autonomic fibers are affected, the patient may have a Horner syndrome. Involvement of the corticospinal tracts results in spastic paraparesis with greater involvement of the legs than the arms.

Vitamin E deficiency affects the posterior columns, spinocerebellar tracts, and dorsal root ganglia.

Primary lateral sclerosis is an upper motor neuron disease. Sensation is normal.

Primary muscular atrophy is a lower motor neuron disease. Often, paraspinous or respiratory muscles are affected. Sensation is normal.

## SPINAL ROOTS AND PERIPHERAL NERVES

**52. B**

C2 supplies sensation to the head through the greater and lesser occipital nerves.

**53. C**

A C5–C6 disc herniation usually affects the C6 nerve. The other statements are true.

**54. D**

This is a C8 radiculopathy. A C8 radiculopathy causes pain in the neck, shoulder, and ulnar part of the forearm. Sensory disturbance is in the fourth and fifth digits and the hypothenar eminence. Weakness is in the intrinsic hand muscles, finger extensors, and finger flexors. This could result from a C7–T1 disc herniation.

A C5 or C6 radiculopathy would affect the biceps and brachioradialis reflexes. A C7 radiculopathy would affect the triceps reflex.

**55. C**

The C8 nerve root exits above the T1 vertebral bone.

In the thoracic, lumbar, and sacral regions, the nerve roots exit below the same numbered vertebral bone (e.g., the T4 nerve root exits below the T4 vertebral bone).

In the cervical region, the nerve roots exit above the vertebral bone of the same number, except that C8 exits between the C7 and T1 vertebral bones. There is no C8 vertebral bone.

**56. B**

The small head of the biceps femoris is the muscle above the knee that is supplied by the peroneal division of the sciatic nerve.

**57. True**

In the peripheral nervous system, foot drop can be caused by lesions of the deep peroneal nerve, common peroneal nerve, sciatic nerve, lumbosacral plexus, or the L5 nerve root. Foot eversion and inversion are intact if the lesion involves only the deep peroneal nerve. Weakness of ankle inversion indicates that the lesion also affects the tibial nerve, which is a branch of the sciatic nerve with L5 innervation. If a patient has foot drop and ankle inversion weakness, the lesion involves the sciatic nerve, lumbosacral plexus, or the L5 nerve root.

(To accurately assess the strength of ankle inversion in a patient with foot drop, the foot should be dorsiflexed while testing inversion.)

**58. C**

The radial nerve gives rise to the posterior interosseus nerve. Lesions of the posterior interosseous nerve cause finger drop.

## CEREBROSPINAL FLUID AND THE VENTRICULAR SYSTEM

**59. C**

The choroid plexus produces CSF at a rate of 20 mL/hr, which is approximately 500 mL/day.

**60. A**

CSF is absorbed from the subarachnoid space into the blood by arachnoid granulations.

CSF is produced by the choroid plexus. It then flows into the lateral ventricles. Next, it travels through the foramen of Monro into the third ventricle. CSF travels from the third ventricle to the fourth ventricle through the Sylvian aqueduct. It then exits the fourth ventricle through the foramina of Luschka and Magendie and travels into the subarachnoid space, where it is absorbed by arachnoid granulations.

## BLOOD–BRAIN BARRIER

**61. D**

The blood–brain barrier results from the presence of tight junctions that link capillary endothelial cells in the brain.

**62. B**

Areas of the brain where the blood–brain barrier is interrupted are called circumventricular organs (see Box 11.2).

*Box 11.2* **CIRCUMVENTRICULAR ORGANS**

- Subfornical organ
- Median eminence
- Neurohypophysis
- Vascular organ of lamina terminalis
- Pineal body
- Area postrema

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**63. B**

The area postrema, which is one of the circumventricular organs, is known as the chemotactic trigger zone because it detects toxins that cause vomiting. It is located at the caudal aspect of the fourth ventricle. It has a high density of dopamine neurons, particularly $D_2$ receptors. Medications that block dopamine $D_2$ receptors prevent vomiting.

## HYPOTHALAMUS

**64. D**

The suprachiasmatic nucleus, which is in the anterior hypothalamus, receives input from retinal ganglion cells via the retinohypothalamic tract. It acts as a circadian clock, regulating circadian rhythms. Release of GABA from the suprachiasmatic nucleus inhibits melatonin release from the pineal gland.

Neurons in the arcuate nucleus secrete growth hormone–releasing hormone. Neurons that secrete dopamine are also present in the arcuate nucleus.

Neurons in the medial preoptic nucleus secrete gonadotropin-releasing hormone.

(The anterior nucleus is discussed in Question 65.)

**65. C**

The anterior nucleus affects temperature and stimulates the parasympathetic nervous system.

The lateral nucleus affects appetite.

The paraventricular nucleus provides most of the innervation to preganglionic sympathetic neurons.

The supraoptic and paraventricular nuclei contain neurons that secrete oxytocin and vasopressin into the posterior pituitary.

# 12.

# NEUROCHEMISTRY

## QUESTIONS

**1. Which of the following structures provides most of the cortical cholinergic projections?**

A. Basal nucleus of Meynert
B. Pedunculopontine nucleus
C. Substantia nigra pars compacta
D. Substantia nigra pars reticulata

**2. What is the rate-limiting factor in acetylcholine (ACh) synthesis?**

A. Amount of choline
B. Availability of choline acetyltransferase
C. Availability of acetyl coenzyme A (acetyl-CoA)
D. Availability of acetylcholinesterase

**3. Which of the following causes increased ACh release?**

A. Botulism
B. Lambert–Eaton syndrome
C. Tick paralysis
D. Black widow spider venom (latrotoxin)
E. Curare

**4. True or false?**

Muscarinic receptors are more common in the brain than nicotinic receptors.

**5. What is the result of depolarization of the nicotinic receptor?**

A. Activation of adenyl cyclase
B. Activation of phospholipase
C. Increased chloride conductance
D. Increased sodium conductance

**6. Monoamine oxidase (MAO) and catechol-*O*-methyltransferase (COMT) convert which of the following neurotransmitters to homovanillic acid (HVA)?**

A. Norepinephrine
B. Epinephrine
C. Dopamine
D. Serotonin

**7. In the synthesis of dopamine, what is the rate-limiting enzyme?**

A. Dopamine β-hydroxylase
B. Dopa decarboxylase
C. MAO types A and B
D. Tyrosine hydroxylase

**8. In which structure is norepinephrine most prevalent?**

A. Dorsal raphe nuclei
B. Hypothalamus
C. Locus ceruleus
D. Nucleus basalis of Meynert

**9. True or false?**

There is no reuptake mechanism for epinephrine.

**10. Dopamine excess results in the positive symptoms of schizophrenia through which of the following pathways?**

A. Mesocortical pathway
B. Mesolimbic pathway
C. Nigrostriatal pathway
D. Tuberoinfundibular pathway

**11. Dopamine excess results in tardive dyskinesia through which of the following pathways?**

A. Mesocortical pathway
B. Mesolimbic pathway
C. Nigrostriatal pathway
D. Tuberoinfundibular pathway

**12. Which of the following is *not* derived from tyrosine?**

A. Norepinephrine
B. Epinephrine
C. Dopamine
D. Serotonin

**13. Where is serotonin produced?**

A. Locus ceruleus
B. Medial forebrain bundle
C. Nucleus accumbens
D. Raphe nuclei

**14. Where are serotonin receptors *least* likely to be found?**

A. Heart
B. Gastrointestinal tract
C. Platelets
D. Sexual organs

**15. At which serotonin receptor does ondansetron act?**

A. $5\text{-HT}_{1a}$
B. $5\text{-HT}_{1b/d}$
C. $5\text{-HT}_{2a}$
D. $5\text{-HT}_{3}$

**16. What is the mechanism of caffeine?**

A. Adenosine antagonist
B. Glutamate agonist
C. Histamine agonist
D. Orexin antagonist

**17. γ-Aminobutyric acid (GABA) is synthesized from which of the following?**

A. Glutamate
B. Glycine
C. Tyrosine
D. Tryptophan

**18. Which of the following is *not* a binding site on the $GABA_A$ receptor?**
A. Barbiturate site
B. Glycine site
C. Steroid site
D. Picrotoxin site

**19. Which of the following is an agonist of the $GABA_B$ receptor?**
A. Baclofen
B. Clobazam
C. Lorazepam
D. Phenobarbital

**20. Which of the following is synthesized from arginine?**
A. Adenosine
B. Histamine
C. Nitric oxide
D. Taurine

**21. Which of the following is most likely to act as an excitatory neurotransmitter?**
A. GABA
B. Glycine
C. Histamine
D. Taurine

**22. What type of cell is responsible for most of the reuptake of glutamate?**
A. Astrocytes
B. Ependymal cells
C. Oligodendrocytes
D. Neurons

**23. Which receptor is ligand gated and voltage sensitive?**
A. α-Amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptor
B. Histamine $H_1$ receptor
C. Kainate receptor
D. *N*-methyl-ᴅ-aspartate (NMDA) receptor

**24. Which of the following is an obligatory co-agonist to the NMDA receptor?**
A. Adenosine
B. Calcium
C. Glycine
D. Magnesium

**25. Fill in the blank: Activation of NMDA receptors requires removal of the ______________ block.**
A. Calcium
B. Magnesium
C. Potassium
D. Sodium

**26. ʟ-Aromatic amino acid decarboxylase, glutamic acid decarboxylase, and GABA transaminase require which of the following as a cofactor?**
A. Copper
B. Oxygen
C. Vitamin $B_6$
D. Vitamin C

**27. Which of the following diseases is associated with reduced levels of glycine in the spinal cord and is treated with benzodiazepines?**
A. Hyperekplexia
B. Stiff-person syndrome
C. Paroxysmal kinesigenic dyskinesia
D. Neuromyotonia

**28. Which of the following is an antagonist of the glycine receptor?**
A. Bicuculline
B. Picrotoxin
C. Strychnine
D. Succinic acid

**29. Historically, Rasmussen encephalitis has been associated most closely with antibodies to which of the following receptors?**
A. $GABA_A$
B. $GABA_B$
C. Glutamate
D. Glycine

**30. Long-term potentiation and long-term depression are dependent on which receptor?**
A. ACh
B. GABA
C. Glycine
D. NMDA

**31. Which of the following structures has the highest concentration of histamine?**
A. Locus ceruleus
B. Dorsal raphe nuclei
C. Nucleus basalis of Meynert
D. Hypothalamus

**32. Which of the following is *not* a function of astrocytes?**
A. Uptake glutamate and convert it to glutamine
B. Maintain the normal concentration of potassium in the brain
C. Guide migrating neurons during embryonic development
D. Contribute to the blood–brain barrier
E. React to injury by causing gliosis
F. All of the above are functions of astrocytes.

**33. Which of the following is the precursor of cholesterol and fatty acids?**
A. Acetyl-CoA
B. Mevalonic acid
C. Phosphatidic acid
D. Ceramide

# NEUROCHEMISTRY

## ANSWERS

**1. A**

The basal nucleus of Meynert is the source of most cortical cholinergic projections. Patients with Alzheimer disease have loss of neurons in this region.

**2. A**

ACh is synthesized from choline and acetyl-CoA by choline acetyltransferase. The amount of choline is the rate-limiting factor.

ACh is degraded in the synaptic cleft by acetylcholinesterase. It is broken down into choline and acetate. Reuptake of choline occurs at the presynaptic terminal.

**3. D**

Black widow spider venom (latrotoxin) increases ACh release.

Curare is a non-depolarizing neuromuscular blocker; it prevents ACh from binding to the nicotinic ACh receptor.

Botulism, Lambert–Eaton syndrome, and tick paralysis are associated with decreased ACh release.

**4. True**

Muscarinic receptors are more common in the brain than nicotinic receptors. The M1 subtype of muscarinic receptors is the most common subtype in the central nervous system. It is found in the cerebral cortex, hippocampus, striatum, and thalamus at postsynaptic locations. In the peripheral nervous system, postganglionic parasympathetic terminals and postganglionic sympathetic sweat glands have muscarinic receptors.

The neuromuscular junction and adrenal medulla have nicotinic receptors.

**5. D**

Nicotinic receptors are ligand-gated ion channels. Depolarization of the nicotinic receptor results in increased sodium conductance.

Mutations in the nicotinic receptor have been found in patients with autosomal dominant sleep-related hypermotor epilepsy (formerly autosomal dominant nocturnal frontal lobe epilepsy). These patients tend to respond well to the sodium channel blocker oxcarbazepine (and to carbamazepine).

The muscarinic acetylcholine receptor is a G protein-coupled receptor.

**6. C**

MAO and COMT convert dopamine to HVA.

Dopamine β-hydroxylase converts dopamine to norepinephrine (see Table 12.1).

*Table 12.1* **NEUROTRANSMITTER BREAKDOWN PRODUCTS**

| NEUROTRANSMITTER | BREAKDOWN PRODUCT |
|---|---|
| **Dopamine** | **Homovanillic acid (HVA)** |
| **Serotonin** | **5-Hydroxyindoleacetic acid (5-HIAA)** |
| **Norepinephrine** | **Vanillylmandelic acid (VMA)** |

**7. D**

Conversion of tyrosine to L-dopa by tyrosine hydroxylase is the rate-limiting step in the synthesis of dopamine. L-Dopa is then converted to dopamine by dopa decarboxylase.

Tyrosine hydroxylase deficiency causes a dopa-responsive dystonia (DYT5b).

**8. C**

Norepinephrine is most prevalent in the locus ceruleus.

**9. True**

Epinephrine is synthesized from norepinephrine by phenylethanolamine *N*-methyltransferase, which is found in certain neurons and in the adrenal medulla. There is no reuptake mechanism for epinephrine. It is broken down by MAO and COMT to vanillylmandelic acid.

**10. B**

There are four major dopamine pathways: mesolimbic, mesocortical, nigrostriatal, and tuberoinfundibular.

The mesolimbic pathway mainly arises from the ventral tegmental area and projects to regions of the limbic system, such as the nucleus accumbens. This pathway is involved in motivation/reward and addiction. It is thought that dopamine excess in the mesolimbic tract causes the positive symptoms of schizophrenia, such as hallucinations.

The mesocortical pathway also mainly arises from the ventral tegmental area, but it projects to the prefrontal cortex. It is involved in cognitive functions, such as

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attention, working memory, and executive function. Its dysfunction causes cognitive symptoms and negative symptoms of schizophrenia.

The nigrostriatal pathway is involved in the regulation of movement. It travels from the substantia nigra pars compacta to the caudate and putamen. Dopamine depletion in this pathway causes parkinsonism.

The tuberoinfundibular pathway regulates the secretion of prolactin from the anterior pituitary gland. Its dysfunction causes hyperprolactinemia.

**11. C**

It is thought that dopamine excess in the nigrostriatal tract causes tardive dyskinesia.

Dopamine neurons in the tuberoinfundibular pathway prevent prolactin secretion. These neurons project from the hypothalamus to the anterior pituitary. Antipsychotics that block dopamine receptors can result in hyperprolactinemia because of this pathway.

**12. D**

Serotonin is derived from tryptophan.

Norepinephrine, epinephrine, and dopamine are derived from tyrosine.

**13. D**

Serotonin is produced in the raphe nuclei. Raphe neurons project through the medial forebrain bundle to multiple areas (i.e., frontal cortex, hippocampus, hypothalamus, striatum, and thalamus).

In the pineal gland, serotonin is converted to melatonin.

**14. A**

Serotonin receptors are least likely to be found in the heart. They are found in the gastrointestinal tract, platelets, and sexual organs.

**15. D**

Ondansetron is a 5-HT$_3$ antagonist. The 5-HT$_3$ receptor is in the area postrema/chemotactic trigger zone. Stimulation of this receptor causes projectile vomiting. Most serotonin receptors are G protein coupled; however, the 5-HT$_3$ receptor is ligand gated.

Buspirone is a 5-HT$_{1a}$ receptor agonist.

Triptans are agonists at 5-HT$_{1b/d}$ receptors.

The 5-HT$_{2a}$ receptor is one of the receptors in which hallucinogens such as lysergic acid diethylamide (LSD) act. Some atypical antipsychotics, such as risperidone, are antagonists to this receptor.

**16. A**

Caffeine is an adenosine antagonist.

The orexin receptor antagonist suvorexant is a treatment for insomnia.

Riluzole is a sodium glutamate antagonist that is used to treat amyotrophic lateral sclerosis. Specifically, it inactivates voltage-gated sodium channels and prevents glutamate release.

**17. A**

GABA is synthesized from glutamate by glutamic acid decarboxylase (GAD). GABA is metabolized by GABA transaminase. Vigabatrin inhibits GABA transaminase, causing an increase in GABA.

**18. B**

There is no glycine binding site on the GABA$_A$ receptor. There is a glycine binding site on the NMDA receptor (see Box 12.1).

***Box 12.1*** **POSSIBLE BINDING SITES ON THE GABA$_A$ RECEPTOR**

- GABA
- Barbiturate
- Benzodiazepine
- Picrotoxin
- Steroid
- Volatile anesthetic

Muscimol is an agonist and bicuculline is an antagonist at the GABA binding site on the GABA$_A$ receptor.

Picrotoxin, which is a chloride channel blocker, is a noncompetitive antagonist of GABA.

Bicuculline and picrotoxin are used in models of epilepsy.

Benzodiazepines, barbiturates, anesthetics, and neurosteroids act at allosteric modulatory sites on the GABA$_A$ receptor.

Zolpidem and zaleplon are nonbenzodiazepines that bind to the benzodiazepine site on the GABA$_A$ receptor.

**19. A**

Baclofen is an agonist of the GABA$_B$ receptor.

Clobazam, lorazepam, and phenobarbital all act at the GABA$_A$ receptor.

**20. C**

Nitric oxide, a signaling molecule in the brain, is synthesized from arginine.

**21. C**

Histamine, which is a biogenic amine, is an excitatory neurotransmitter.

With some exceptions, GABA, glycine, and taurine are usually inhibitory neurotransmitters. For example, in the immature brain, GABA can be excitatory.

**22. A**

Astrocytes are responsible for glutamate reuptake. In the astrocyte, glutamate may be converted to glutamine, which may be exported to the extracellular space and then transferred to neurons.

**23. D**

The NMDA receptor is ligand gated and voltage sensitive.

Histamine receptors, which include $H_1$, $H_2$, $H_3$, and $H_4$, are G protein-coupled receptors. Diphenhydramine and cetirizine are examples of $H_1$ receptor antagonists. Ranitidine, famotidine, and cimetidine are examples of $H_2$ receptor antagonists. Pitolisant, which is a treatment for narcolepsy, is an $H_3$ receptor antagonist/inverse agonist. (There are $H_4$ receptor antagonists in clinical trials.)

**24. C**

The NMDA receptor has binding sites for glutamate and glycine. Glycine is an obligatory co-agonist with glutamate at the NMDA receptor, where it has an excitatory role.

There is also a polyamine binding site on the NMDA receptor.

**25. B**

Activation of the NMDA receptor requires binding of glutamate and glycine, depolarization, and removal of the magnesium block. Magnesium is a voltage-dependent blocker. When depolarization occurs, the block is removed. Zinc also decreases flow through the NMDA receptor.

Calcium and sodium flow through the open NMDA receptor channel. Among the glutamate receptors (i.e., AMPA, kainate, and NMDA), the NMDA receptor is the most permeable to calcium.

The mushroom *Amanita muscaria* contains an NMDA receptor agonist. There are a number of NMDA receptor antagonists (see Box 12.2).

*Box 12.2* NMDA RECEPTOR ANTAGONISTS

- Amantadine
- Dextromethorphan
- Felbamate
- Ketamine
- Memantine
- Phencyclidine (PCP)

The anti-seizure medication perampanel is a noncompetitive AMPA receptor antagonist.

**26. C**

L-Aromatic amino acid decarboxylase, GAD, and GABA transaminase require vitamin $B_6$ as a cofactor.

L-Aromatic amino acid decarboxylase deficiency manifests in infancy with developmental delay, abnormal tone (truncal hypotonia and limb hypertonia), choreoathetosis, and oculogyric crises. Patients may also have autonomic dysfunction.

GAD converts glutamic acid to GABA.

GABA transaminase metabolizes GABA (to succinic semialdehyde).

**27. A**

Hyperekplexia is associated with reduced glycine levels in the spinal cord. Glycine is an inhibitory neurotransmitter in the spinal cord. When glycine binds to its receptor, there is increased conductance of chloride. This results in hyperpolarization of the membrane, so it is less likely to depolarize.

GAD antibodies are found in patients with stiff-person syndrome.

Paroxysmal kinesigenic dyskinesia can be caused by mutations in the *PRRT2* gene.

Potassium channel antibodies have been found in some patients with neuromyotonia.

**28. C**

Strychnine is an antagonist of the glycine receptor. It can be found in rat poison. It causes muscle spasms that can result in rhabdomyolysis. Strychnine blocks glycine receptors, inhibiting opening of the chloride channel. Lack of normal inhibition leads to hyperexcitability.

**29. C**

Some patients with Rasmussen encephalitis have antibodies to the glutamate receptor.

**30. D**

Long-term potentiation and long-term depression are dependent on the NMDA receptor. Long-term potentiation is a long-lasting increase in synaptic strength that occurs when synapses are repeatedly stimulated. Long-term depression is a long-lasting decrease in synaptic strength that occurs when synapses are less frequently stimulated. Both processes play important roles in learning and memory formation.

**31. D**

The highest concentration of histamine is in the hypothalamus. Specifically, histaminergic neurons are found in the lateral tuberomammillary nucleus of the hypothalamus. Histamine is synthesized from histidine.

Norepinephrine is found in the locus ceruleus.

Serotonin is found in the dorsal raphe nuclei.

ACh is found in the nucleus basalis of Meynert.

**32. F**

Astrocytes are important in potassium homeostasis. They are characterized by large negative membrane potentials that allow them to buffer extracellular potassium. Astrocytes also help buffer extracellular pH.

**33. A**

Acetyl-CoA is the precursor of cholesterol and fatty acids. It is a two-carbon donor.

In cholesterol synthesis, two acetyl-CoA molecules are condensed to form acetoacetyl-CoA. This is condensed with another acetyl-CoA molecule to form 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA). HMG-CoA is converted to mevalonic acid by HMG-CoA reductase, which is the rate-limiting enzyme in cholesterol synthesis.

The rate-limiting step in fatty acid synthesis is conversion of acetyl-CoA into malonyl-CoA by acetyl-CoA carboxylase. Excess acetyl-CoA is converted into fatty acids.

Phosphatidic acid is the precursor of glycerolipids, which are derivatives of glycerol and fatty acids.

Ceramide is the precursor of sphingolipids.

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# 13.

# NEUROGENETICS

## QUESTIONS

1. **A child is diagnosed with a disease. None of her three siblings have the disease, but two are found to be carriers. Neither of her parents has the disease. (Their carrier status was not tested.) What is the mode of inheritance?**
   A. Autosomal dominant
   B. Autosomal recessive
   C. X-linked recessive
   D. X-linked dominant

2. **Which of the following is *not* an autosomal dominant disorder?**
   A. Achondroplasia
   B. Kennedy disease
   C. Neurofibromatosis type 2 (NF2-related schwannomatosis)
   D. Tuberous sclerosis complex

3. **Which of the following is *not* an X-linked recessive disorder?**
   A. Duchenne muscular dystrophy
   B. Lesch–Nyhan disease
   C. Menkes disease
   D. Ornithine transcarbamoylase deficiency
   E. Phenylketonuria

4. **What is the most common mode of inheritance of intellectual disability?**
   A. Autosomal dominant
   B. Autosomal recessive
   C. X-linked

5. **Which of the following diseases is *not* X-linked dominant?**
   A. Aicardi syndrome
   B. Fabry disease
   C. Incontinentia pigmenti
   D. Rett syndrome

6. **A child develops a disease at age 2 years and has severe symptoms. His father began having similar symptoms when he was 20 years old, and his symptoms are not severe. The child's grandfather was found to have the disease at age 75 years but has minimal symptoms. What is the term used for worsening symptoms with each generation?**
   A. Anticipation
   B. Expressivity
   C. Imprinting
   D. Penetrance

7. **What is the term for a disease that is caused by a combination of genetic and environmental factors?**
   A. Complex trait
   B. Polygenic disease
   C. Pseudodominant inheritance
   D. Endophenotype
   E. Compound heterozygote

8. **Which of the following is *not* a mitochondrial disease?**
   A. Chronic progressive external ophthalmoplegia
   B. Leber hereditary optic neuropathy (LHON)
   C. Neurogenic muscle weakness, ataxia, and retinitis pigmentosa
   D. Myoneuro-gastrointestinal encephalopathy
   E. Nonketotic hyperglycinemia

9. **Which of the following statements is *false*?**
   A. Mitochondrial diseases may demonstrate autosomal recessive inheritance.
   B. Heteroplasmy plays a role in mitochondrial disease.
   C. The same mitochondrial DNA (mtDNA) sequence may occur in patients with different diseases.
   D. Patients with the same mitochondrial disease may have different mtDNA mutations.
   E. Mitochondrial diseases often have strong penetrance.

10. **Which of the following diseases is *not* caused by a trinucleotide repeat?**
    A. Joubert syndrome
    B. Kennedy disease
    C. Fragile X syndrome
    D. Dentatorubral–pallidoluysian atrophy (DRPLA)

11. **Which of the following diseases is caused by a GAA triplet repeat expansion?**
    A. Friedreich ataxia
    B. Huntington disease
    C. Myotonic dystrophy type 1
    D. Oculopharyngeal muscular dystrophy

12. **Which of the following diseases is caused by expansion of a tetranucleotide repeat?**
    A. Facioscapulohumeral muscular dystrophy (FSHD)
    B. Machado–Joseph disease
    C. Myotonic dystrophy type 2
    D. Spinocerebellar ataxia type 10 (SCA10)

13. **Which of the following diseases is caused by expansion of a hexanucleotide repeat?**
    A. Unverricht–Lundborg disease
    B. Chromosome 9p–linked frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS)

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C. Spinocerebellar ataxia type 1
D. Spinocerebellar ataxia type 8

**14. Which of the following diseases is *not* a channelopathy?**
A. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
B. Episodic ataxia type 1 (EA1)
C. EA2
D. Familial hemiplegic migraine
E. Hyperekplexia

**15. In a child with global developmental delay, which of the following should be performed first if no specific etiology is suspected and neither whole exome nor whole genome testing is feasible?**
A. Chromosomal microarray (CMA)
B. Plasma amino acids and urine organic acids
C. Ammonia level
D. Karyotype

**16. In which of the following diseases does imprinting *not* occur?**
A. Prader–Willi syndrome (PWS)
B. Myoclonus dystonia syndrome (dystonia 11)
C. Beckwith–Wiedemann syndrome
D. Russell–Silver syndrome
E. Huntington disease

**17. In which of the following conditions is anticipation *least* likely to occur?**
A. Dentatorubral-pallidoluysian atrophy
B. Fragile X syndrome
C. Spinocerebellar ataxia type 1
D. Spinocerebellar ataxia type 6

**18. A 2-year-old girl is brought to the clinic because of developmental delay. The family reports that she has no speech and does not sleep well but is very happy. On examination, she is laughing and drooling. She has a broad mouth with widely spaced teeth. She is microcephalic, hypotonic, and ataxic.**

**a. What other condition is common in this syndrome?**
A. Epilepsy
B. Prolonged QT interval
C. Cardiac defects
D. Hypocalcemia

**b. Where is the genetic defect in most patients with this syndrome?**
A. Chromosome 5q
B. Chromosome 7q
C. Chromosome 15q
D. Chromosome 22q

**19. A 7-year-old boy presents with school difficulties and behavior problems. The parents report temper tantrums and excessive eating. They say that he had difficulties feeding as a neonate but now he will not stop. They put a lock on the refrigerator at night to prevent him from eating. Although he is having learning difficulties, he is excellent at putting puzzles together. On examination, he is obese, has almond-shaped eyes, and has small hands and feet. Which test is most likely to yield the diagnosis?**
A. Testing for expansion of CGG repeats on the X chromosome
B. Methylation analysis at 5' *SNRPN* (small nuclear ribonucleoprotein polypeptide N)
C. Testing for expansion of CTG repeats in *DMPK*
D. Testing for Williams–Beuren syndrome critical region

**20. Which of the following disorders is *least* likely to occur in Down syndrome?**
A. Moyamoya syndrome
B. Atlanto-axial subluxation
C. Obstructive sleep apnea (OSA)
D. Epileptic spasms
E. Peripheral neuropathy

**21. An 8-year-old girl presents with school difficulties. The parents report no social problems. She is gregarious and empathetic. However, she is unable to do the work the other children are doing. She has a good short-term memory but significant problems with visuospatial skills. Her past medical history is remarkable for supravalvular aortic stenosis and hypercalcemia. What is the most likely diagnosis?**
A. Angelman syndrome
B. DiGeorge syndrome
C. Turner syndrome
D. Williams syndrome

**22. An 11-year-old boy is brought to the clinic because of difficulties in school. The teacher thinks he has autism. His mother states that she was diagnosed with a learning disability. The family history is remarkable for a maternal grandfather with intention tremor and gait unsteadiness. On examination, the boy has a long face and protuberant ears. What is the diagnosis?**
A. Fragile X syndrome
B. Klinefelter syndrome
C. 47,XYY syndrome
D. Sotos syndrome

**23. A 2-year-old girl presents with loss of developmental milestones. The parents said she was developing normally until age 18 months. Then her speech decreased, and it is now nonexistent. She no longer plays with toys; instead, she wrings her hands. The parents have also noted unusual breathing. A defect in which of the following genes is most likely responsible?**
A. *MECP2*
B. *UBE3A*
C. *ELN*
D. *CDKL5*

**24. An infant with a submucosal cleft palate, hypotonia, and tetralogy of Fallot develops seizures. Laboratory studies show hypocalcemia. Which diagnosis is most likely?**

A. Trisomy 21
B. DiGeorge syndrome
C. Prader–Willi syndrome
D. Congenital myotonic dystrophy

**25. Which of the following is *least* likely to be detected by CMA?**

A. Chromosomal aneuploidy
B. Balanced chromosomal translocation
C. Unbalanced chromosomal translocation
D. Chromosomal copy number variation

**26. Which of the following is most likely to detect repeat expansions?**

A. Methylation-sensitive analysis
B. Multiplex ligation-dependent probe amplification
C. Southern blot
D. Whole exome sequencing

**27. Mutations in multiple genes can cause nemaline myopathy. What concept is this an example of?**

A. Genetic heterogeneity
B. Mosaicism
C. Phenotypic pleiotropy
D. X-inactivation

**28. What is the mechanism of action of nusinersen?**

A. It increases transcription of the *SMN 1* gene.
B. It is a safe virus that delivers the *SMN 1* gene.
C. It is a safe virus that delivers the *SMN 2* gene.
D. It is a *SMN-2* directed antisense oligonucleotide.

**29. Which of the following would be most helpful for certain patients with Duchenne muscular dystrophy?**

A. Cerliponase alfa
B. Eteplirsen
C. Omaveloxolone
D. Trofinetide

# NEUROGENETICS

## ANSWERS

**1. B**

This disease is an autosomal recessive condition. Twenty-five percent of the children in this family have the disease, 50% are carriers, and 25% are healthy. If tested, both parents would be found to be carriers. In autosomal recessive conditions, genes from both parents at a particular locus must be mutated to cause the disease. Both genders are equally affected. Autosomal recessive conditions are more likely in consanguineous unions. A recessive trait that is common, such as blood type O, can result in what appears to be a dominant inheritance pattern.

If this were an autosomal dominant disease, one of the parents would have the disease, and 50% of the children would be affected. Only one copy of the mutation would be needed to express the trait. Both genders are equally affected in autosomal dominant diseases.

A mother carrying an X-linked recessive disease will pass the affected X chromosome to 50% of her children. Half of her sons will be affected by the disease. The mother is usually an asymptomatic carrier. A female may be affected due to X-inactivation or if her father has the condition and her mother is a carrier.

X-linked dominant diseases usually affect males more severely than females. In some X-linked dominant diseases, affected males do not survive to birth. Each child of an affected female has a 50% chance of having the condition, regardless of gender. In the case of an affected male, all of his daughters but none of his sons will be affected.

In X-linked conditions, there is no male-to-male transmission. There can be an appearance of male-to-male transmission in the unusual circumstance in which an affected male has a child with a carrier female.

**2. B**

Spinobulbar muscular atrophy, also known as Kennedy disease, is X-linked recessive.

Tuberous sclerosis complex, neurofibromatosis type 1, neurofibromatosis type 2 (NF2-related schwannomatosis), and achondroplasia are autosomal dominant.

**3. E**

Phenylketonuria is autosomal recessive.

Lesch–Nyhan disease, Menkes disease, ornithine transcarbamoylase deficiency, and Duchenne muscular dystrophy are X-linked recessive. Adrenoleukodystrophy and Pelizaeus–Merzbacher disease are also X-linked recessive.

**4. C**

If inherited, intellectual disability most often is inherited in an X-linked pattern.

**5. B**

Fabry disease is X-linked recessive.

Aicardi disease, incontinentia pigmenti, and Rett syndrome are X-linked dominant.

**6. A**

This is anticipation, which occurs in some triplet repeat diseases, such as Huntington disease and myotonic dystrophy type 1. Subsequent generations have more copies of the triplet repeat, which is associated with more severe disease and an earlier presentation.

Oculopharyngeal muscular dystrophy is a triplet repeat disease that does *not* demonstrate anticipation. It is caused by mutations in the gene *PABPN1*. Originally, the disease was said to be a GCG triplet repeat disease. However, GCA, GCT, GCC, and GCG all encode alanine; therefore, it is now said to be due to expansion of GCN repeats ("N" indicates any base).

**7. A**

A disease that is caused by a combination of genetic and environmental factors is a complex trait. Examples include Alzheimer disease, Parkinson disease, stroke, migraine, multiple sclerosis, ALS, and restless leg syndrome.

Polygenic diseases are diseases caused by multiple genes. One example is cleft palate.

Pseudodominant inheritance is the term for a condition that gives the appearance of being an autosomal dominant disease but is not. For instance, an autosomal recessive condition that occurs in multiple generations can demonstrate pseudodominant inheritance. This may result from a high carrier frequency, or it may occur if the parents are genetically related.

An endophenotype is a characteristic that is associated with a condition but does not result from that condition.

A compound heterozygote is an individual who has two different abnormal alleles at a specific locus, one on each chromosome of a pair. This can be seen in autosomal recessive conditions.

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**8. E**

Nonketotic hyperglycinemia is *not* a mitochondrial disease (see Box 13.1).

***Box 13.1*** **MITOCHONDRIAL DISEASES**

- Kearns–Sayre syndrome
- Leber hereditary optic neuropathy (LHON)
- Leigh syndrome
- Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)
- Myoclonic epilepsy and ragged red fibers (MERRF)
- Myoneuro-gastrointestinal encephalopathy (MNGIE)
- Neurogenic muscle weakness, ataxia, and retinitis pigmentosa (NARP)
- *POLG*-related disorders
  - Alpers–Huttenlocher syndrome
  - Childhood myocerebrohepatopathy spectrum disorders
  - Myoclonic epilepsy myopathy sensory ataxia
  - *POLG*-related ataxia neuropathy spectrum disorders
  - Progressive external ophthalmoplegia

For unclear reasons, Leber hereditary optic neuropathy (LHON) affects males more than females. LHON can be treated with idebenone, which has antioxidant properties and can act as a mitochondrial electron carrier.[1]

Mutations in both nuclear- and mitochondrial-encoded genes can cause Leigh syndrome. The most common cause is a defect in complex IV (cytochrome *c* oxidase [COX]). The most common cause of COX-deficient Leigh syndrome is a mutation in *SURF1*.

Most cases of MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes) are caused by mutations in *MT-TL1* (transfer RNA mitochondrial, leucine 1).

**9. E**

Mitochondrial diseases often have reduced penetrance.

Heteroplasmy occurs when there are both normal mitochondria and mitochondria with mutant DNA within a cell. A mother passes on her mutant mtDNA, but her children have different amounts of the mutant mtDNA, and the amount also varies in different organs of the same individual. In addition, the proportion of mutant mitochondria can change with time.

If a disease results from a mutation in the mitochondrial genome, the disease demonstrates matrilineal inheritance because males do not pass mitochondria to their children. However, mitochondria also use some proteins that have been encoded by nuclear DNA. Defects in these proteins can cause diseases that follow nonmatrilineal inheritance patterns.

Genotype–phenotype correlations are poor with mitochondrial diseases. An mtDNA sequence may occur in patients with different diseases, and patients with the same mitochondrial disease may have different mtDNA mutations.

**10. A**

Joubert syndrome is not a trinucleotide disease.

In Kennedy disease, the triplet repeat is CAG. In fragile X syndrome, the triplet repeat is CGG. In DRPLA, the triplet repeat is CAG (see Table 13.1).

***Table 13.1*** **SELECTED TRIPLET REPEAT DISEASES**

| DISEASE | TRIPLET REPEAT |
|---|---|
| **Dentatorubral–pallidoluysian atrophy (DRPLA)** | CAG |
| **Fragile X syndrome** | CGG |
| **Kennedy disease** | CAG |

**11. A**

Friedreich ataxia is caused by a GAA triplet repeat expansion. It results from mutations in the *FXN* (formerly *FRDA*) gene on chromosome 9q. Mutations in this gene cause decreased production of frataxin, which acts as a mitochondrial iron chaperone. (A therapy for Friedreich ataxia is discussed in Question 29.)

Huntington disease is caused by an expansion of the CAG triplet repeat in the gene *HTT* on chromosome 4. It is autosomal dominant.

Myotonic dystrophy type 1 is caused by expansion of the CTG repeat in the *DMPK* gene on chromosome 19. It is autosomal dominant.

Oculopharyngeal muscular dystrophy is caused by expansion of the triplet repeat GCN ("N" indicates any base) in the gene *PABPN1*, which encodes the polyadenylate binding protein nuclear 1.

**12. C**

Myotonic dystrophy type 2, which has also been called proximal myotonic myopathy (PROMM), is a tetranucleotide repeat disease. The repeat is CCTG. The mutated gene is *ZNF9* on chromosome 3, which encodes zinc finger protein 9. (This gene has also been called *CNBP*.)

Machado–Joseph disease, also known as SCA3, is due to an abnormal CAG repeat expansion in the gene *ATXN3*.

SCA10 is a pentanucleotide repeat disease (ATTCT).

Most cases of FSHD result from a *contraction* mutation of *D4Z4* on chromosome 4, resulting in fewer repeats than normal. In addition, a permissive simple sequence length polymorphism and the 4qA variant at the terminus must be present for the disease to manifest clinically. The result of the combination of these genetic features is hypomethylation of the D4Z4 region. This region contains the *DUX4* gene, which encodes double homeobox protein 4 (DUX4). These mutations cause FSHD1. FSHD2 is caused by mutations in the *SMCHD1* gene. Mutations in the *SMCHD1* gene also affect DUX4 expression.[2]

**13. B**

Expansion of a hexanucleotide repeat (GGGGCC) in the gene *C9ORF72* is associated with autosomal dominant FTD and ALS linked to chromosome 9p.[3]

SCA1 and SCA8 are triplet repeat diseases.

Unverricht–Lundborg disease (EPM1) is most often caused by a dodecamer repeat expansion (CCCCGCCCCGCG) in the *CSTB* gene, which encodes cystatin B (see Tables 13.2–13.5).

*Table 13.2* TRIPLET REPEAT DISEASES

| DISEASE | TRIPLET REPEAT |
|---|---|
| **Dentatorubral–pallidoluysian atrophy (DRPLA)** | **CAG** |
| **Fragile X syndrome** | **CGG** |
| **Friedreich ataxia** | **GAA** |
| **Kennedy disease** | **CAG** |
| **Myotonic dystrophy type 1** | **CTG** |
| **Oculopharyngeal muscular dystrophy** | **GCN** |
| **Spinocerebellar ataxia type 1** | **CAG** |

*Table 13.3* TETRANUCLEOTIDE REPEAT DISEASE

| DISEASE | TETRANUCLEOTIDE REPEAT |
|---|---|
| **Myotonic dystrophy type 2** | **CCTG** |

*Table 13.4* PENTANUCLEOTIDE REPEAT DISEASE

| DISEASE | PENTANUCLEOTIDE REPEAT |
|---|---|
| **Spinocerebellar ataxia type 10** | **ATTCT** |

*Table 13.5* HEXANUCLEOTIDE REPEAT DISEASE

| DISEASE | HEXANUCLEOTIDE REPEAT |
|---|---|
| **Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) (on chromosome 9p)** | **GGGGCC** |
| **Spinocerebellar ataxia 36** | **GGCCTG** |

**14. A**

CADASIL is not a channelopathy. It is caused by a mutation in *Notch 3* on chromosome 19p.

Episodic ataxia type 1 (EA1) is caused by a potassium channel defect. Patients with this condition can have myokymia/neuromyotonia as well as ataxia.

Episodic ataxia type 2 (EA2) and familial hemiplegic migraine type 1 (FHM1) are caused by defects in calcium channels. In fact, EA2, FHM1, and spinocerebellar ataxia type 6 (SCA6) are all caused by mutations in *CACNA1A* on chromosome 19, which encodes the transmembrane pore-forming subunit of the P/Q-type voltage-gated calcium channel. SCA6 is associated with an expansion of CAG repeats within the *CACNA1A* coding region.

Whereas FHM1 results from a calcium channel defect, FHM2 is caused by mutations in sodium/potassium adenosine triphosphatase ($Na^+$,$K^+$-ATPase) pumps, and FHM3 is caused by sodium channel mutations (see Table 13.6).

*Table 13.6* GENETIC CAUSES OF FAMILIAL HEMIPLEGIC MIGRAINE SYNDROMES

| CONDITION | MUTATED GENE | DEFECTIVE PROTEIN |
|---|---|---|
| **FHM type 1** | *CACNA1A* | **P/Q-type voltage-gated calcium channel** |
| **FHM type 2** | *ATP1A2* | **$\alpha_2$ Subunit of the $Na^+$, $K^+$-ATPase pump** |
| **FHM type 3** | *SCN1A* | **$\alpha_1$ Subunit of the voltage-gated sodium channel** |

FHM, familial hemiplegic migraine.

Hyperekplexia is caused by defects in the glycine receptor (see Box 13.2).

*Box 13.2* NEUROLOGIC MANIFESTATIONS OF CHANNELOPATHIES

- Ataxia
- Congenital myasthenia syndrome
- Epilepsy
- Excessive pain, insensitivity to pain
- Hyperekplexia
- Migraine
- Myotonia
- Periodic paralysis

Defects in potassium channels can cause periodic paralysis. Potassium channel defects also cause self-limited neonatal epilepsy and epilepsy with dyskinesia. Defects in sodium and chloride channels can cause myotonia. Defects in the *SCN9A* gene cause pain syndromes. Defects in nicotinic acetylcholine receptors can cause congenital myasthenic syndromes. Other nicotinic acetylcholine receptor defects are associated with frontal lobe epilepsy (Tables 13.7 and 13.8).[4]

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*Table 13.7* NEUROLOGIC CONDITIONS RESULTING FROM CHANNELOPATHIES

| CONDITION | DEFECTIVE CHANNELS |
|---|---|
| Ataxia | Calcium, potassium |
| Congenital myasthenia syndrome | Nicotinic acetylcholine |
| Epilepsy | Calcium, GABA, nicotinic acetylcholine, potassium, sodium |
| Excessive pain, insensitivity to pain | Sodium |
| Hyperekplexia | Glycine |
| Migraine | Calcium, sodium |
| Myotonia | Chloride, sodium |
| Periodic paralysis | Calcium, potassium, sodium |

*Table 13.8* CHANNELOPATHIES THAT CAUSE NEUROLOGIC CONDITIONS

| CHANNEL | CONDITIONS |
|---|---|
| Acetylcholine (nicotinic) | Epilepsy, congenital myasthenia |
| Calcium | Ataxia, epilepsy, migraine, periodic paralysis |
| Chloride | Myotonia |
| GABA | Epilepsy |
| Glycine | Hyperekplexia |
| Potassium | Ataxia, epilepsy, periodic paralysis |
| Sodium | Epilepsy, migraine, myotonia, pain syndromes, periodic paralysis |

**15. A**

Of the options listed, CMA should be performed first if no specific etiology for developmental delay is suspected. Karyotyping and subtelomeric fluorescence in situ hybridization (FISH) testing may be performed if CMA is not available.[5]

**16. E**

Imprinting occurs in Prader–Willi, Angelman, Beckwith–Wiedemann, Russell–Silver, and myoclonus dystonia (DYT11 or DYT11-MD) syndromes. Imprinting also occurs with transient neonatal diabetes 1. Imprinting does *not* occur in Huntington disease.

Imprinting occurs when the expression of an allele depends on whether it is maternal or paternal in origin. For instance, in DYT11-MD, the maternal allele typically is methylated, and expression is reduced. Consequently, if a mutation is inherited from the mother, it is less likely to cause disease. As a result, the disease is autosomal dominant with reduced penetrance. In DYT11-MD, the mutated gene is *SGCE*, which encodes ε-sarcoglycan.

Prader–Willi and Angelman syndromes are both due to defects that affect 15q11q13. Imprinting determines the phenotype. Beckwith–Wiedemann and Russel–Silver syndromes can result from defects at 11p15.5.[6]

Imprinting is an epigenetic process. Examples of Mendelian disorders of epigenetic machinery are Sotos, Rubinstein–Taybi, Kabuki, Rett, and CHARGE syndromes.[6]

Anticipation occurs in Huntington disease (i.e., subsequent generations have more severe disease and/or earlier onset of disease). Anticipation is seen in diseases caused by expanded triplet repeats. If a child has a greater number of repeats than the parent, the disease may manifest first in the child, in which case the autosomal dominant inheritance pattern is less evident. In Huntington disease, anticipation is seen more often with paternal transmission than with maternal transmission because instability of the CAG repeat during spermatogenesis produces longer repeats.

**17. D**

SCA6 and oculopharyngeal muscular dystrophy are triplet repeat diseases that do *not* demonstrate anticipation.

Anticipation is seen in DRPLA, fragile X syndrome, and SCA1. It also occurs in Huntington disease and myotonic dystrophy type 1.

SCA5 demonstrates anticipation, but it is *not* the result of a repeat expansion mutation. It is caused by mutations in the gene *SPTBN2*.

**18a. A and 18b. C**

This patient has Angelman syndrome, which is frequently associated with seizures.

Patients with Angelman syndrome appear normal at birth and initially have a normal head circumference. Developmental delay is noted at ages 6–12 months. There is no regression. They are clumsy and unsteady and usually have an ataxic gait. Speech is nonexistent or minimal. Receptive language is better than expressive. They seem happy and smile and/or laugh frequently. They have a short attention span. Magnetic resonance imaging (MRI) results are normal. Patients with Angelman syndrome have a distinctive facial appearance. They have a prominent chin, a wide mouth, and widely spaced teeth. They often drool. Delayed head growth results in microcephaly, usually by age 2 years. These patients tend to have problems sleeping, are often fascinated by water, and are sensitive to heat.[7,8]

The majority of patients with Angelman syndrome develop seizures, typically between ages 1 and 5 years. They may have seizures associated with fever in infancy. Multiple seizure types can be seen, including atypical absence and myoclonic seizures. There are specific electroencephalographic findings in Angelman syndrome, including high-amplitude slow spike-and-wave discharges, notched delta activity, and waves with a triphasic morphology.[8]

Angelman syndrome is caused by decreased expression of the *UBE3A* gene from the maternal chromosome. This can result from any of four mechanisms: deletion of 15q11-q13 from the maternal chromosome, paternal uniparental disomy, an imprinting defect resulting in decreased expression of the maternal copy of *UBE3A*, or mutations in the maternal copy of *UBE3A*. The most common cause is the first listed, deletion of 15q11-q13 from the maternal chromosome. Often, the evaluation begins with methylation studies.[7,8]

**19. B**

This patient has Prader-Willi syndrome (PWS). The first steps in diagnosis are methylation studies and an oligo-SNP combination array. The small nuclear ribonucleoprotein polypeptide N gene (*SNRPN*) is located on chromosome 15q in the region associated with PWS. It is transcribed only from the paternally inherited chromosome.

PWS may result from deletion of 15q11-q13 from the paternal chromosome, maternal uniparental disomy, abnormal imprinting of the PWS region, or a balanced translocation involving chromosome 15. The most common cause is the first one listed, deletion of this region from the paternal chromosome. Methylation studies can demonstrate the absence of paternally imprinted genes at 15q11-13.

Patients with PWS are hypotonic at birth and do not feed well. They have developmental delay. Between ages 6 and 12 years, they develop hyperphagia, which can result in significant obesity. They may develop OSA. Children with PWS have cognitive impairment. Behavior problems such as temper tantrums, obsessive behaviors, skin picking, and difficulties with transitions may occur. Seizures occur in 10–20% of patients. Patients with PWS tend to have a narrow bifrontal diameter, almond-shaped eyes, a thin upper vermillion, and genital hypoplasia. They also have an increased risk for strabismus and scoliosis. Multiple endocrine problems can occur with PWS, including type 2 diabetes mellitus, growth hormone deficiency, central adrenal insufficiency, hypothyroidism, and hypogonadotropic hypogonadism.[9–11]

Neonates with PWS resemble neonates with congenital myotonic dystrophy type 1, which is associated with expansion of a CTG trinucleotide repeat in the *DMPK* gene on chromosome 19q, but the differentiation is easier as the child gets older.

**20. E**

Newborns with Down syndrome (trisomy 21) are hypotonic. Cardiac anomalies are common, especially defects in the atrioventricular septum. Gastrointestinal anomalies are also common, including duodenal atresia, anal atresia, megacolon, and Hirschsprung disease. Polycythemia may occur in neonates. Cataracts, thyroid disease, and hearing defects are also concerns. Fontanelles are slow to close.

Patients with Down syndrome are at increased risk for moyamoya syndrome, atlanto-axial subluxation, OSA, and epileptic spasms. Due to the risk for OSA, a sleep study is recommended between ages 3 and 4 years.[12]

Cardiac abnormalities increase their risk for embolic strokes and brain abscesses.

Neuropathological changes consistent with Alzheimer disease are common in patients with Down syndrome by age 40 years.[13] (The gene for amyloid precursor protein, a risk factor for Alzheimer disease, is on chromosome 21.)

**21. D**

This is Williams syndrome, which is caused by a mutation in the gene encoding elastin on chromosome 7q11. Children with Williams syndrome may have supravalvular aortic stenosis and hypercalcemia. They often have a stellate iris and elfin facies. They are described as hypersocial and musically talented. They commonly have difficulties with visuospatial construction.

The diagnosis of Williams syndrome may be made with FISH or with deletion testing for the Williams–Beuren syndrome critical region on chromosome 7, which includes the elastin gene.

**22. A**

Fragile X is the most common inherited cause of mental retardation and the most common cause of intellectual disability in males.[14] It is associated with an increased number of CGG repeats in the *FMR1* gene on chromosome X. Relatives of patients with fragile X syndrome who have an *FMR1* premutation may develop late-onset cerebellar ataxia and intention tremor. This condition is referred to as fragile X–associated tremor/ataxia syndrome (FXTAS). On MRI, white matter lesions may be seen in the middle cerebellar peduncles, the brainstem, or both.

Patients with Klinefelter syndrome (XXY) have gynecomastia, small testicles, a wide arm span, and cognitive impairment (a relatively low verbal IQ and reading and writing disorders).

Patients with 47,XYY syndrome may have developmental delay and autism spectrum disorder but do not have atypical facial features.

Patients with Sotos syndrome have cerebral gigantism and are large for their size when young.

**23. A**

This patient has Rett syndrome. Most cases of Rett syndrome are caused by defects in *MECP2*, which encodes methyl-CpG-binding protein 2. It is X-linked dominant, so the vast majority of patients are female.

Initial development is normal in patients with Rett syndrome but plateaus between ages 6 and 18 months. This is followed by regression, after which development

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finally stabilizes.[15] Deceleration of head growth, loss of purposeful use of the hands, gait apraxia, and loss of speech are characteristic. Patients develop stereotyped use of the hands, such as hand wringing. Patients may have a prolonged QT interval, abnormal breathing, cold hands and feet, seizures, and scoliosis. The U.S. Food and Drug Administration approved a treatment for Rett syndrome; this is discussed below.

Mutations in *CDKL5*, which encodes cyclin-dependent–like kinase 5, cause CDKL5 deficiency disorder. This is a developmental epileptic encephalopathy. Similar to Rett syndrome, CDKL5 deficiency disorder is X-linked dominant. Developmental delays and seizures tend to be more severe in CDKL5 deficiency disorder than in Rett syndrome. In CDKL5 deficiency syndrome, seizures begin in infancy and are difficult to control.

*ELN* encodes elastin. Defects in *ELN* are associated with Williams syndrome.

Defects in *UBE3A* are associated with Angelman syndrome.

**24. B**

Trisomy 21, DiGeorge syndrome, PWS, and congenital myotonic dystrophy all cause neonatal hypotonia. This patient has DiGeorge syndrome.

DiGeorge syndrome results from developmental defects of the third and fourth pharyngeal pouches and the fourth branchial arch. It is caused by a mutation at 22q11.2.

There are other conditions caused by deletions at 22q11.2, including velocardiofacial syndrome and Cayler cardiofacial syndrome. Deletions at 22q11.2 result in cardiac and palate anomalies, immunodeficiency due to thymic hypoplasia, distinctive facial features, and learning problems. Hypocalcemia and seizures also occur with this condition.

**25. B**

Chromosomal microarray can detect chromosomal aneuploidy (chromosomal structural abnormalities such as monosomy or trisomy), unbalanced chromosomal translocation (rearrangement of chromosome structure resulting in loss or gain of genetic material), and chromosomal copy number variation (duplication or deletion of a region of a chromosome); however, it can miss balanced chromosomal translocation (a rearrangement of chromosome structure in which there is no loss or gain of genetic material). Karyotype is superior to chromosomal microarray at detecting balanced chromosomal translocation.[14] Karyotype is also necessary to detect ring chromosomes.[16]

**26. C**

Southern blot would be the most likely to detect repeat expansions.[14]

Methylation-sensitive analysis detects chromosomal methylation (the addition of a methyl group to cytosine), which is how imprinting occurs.

Multiplex ligation-dependent probe amplification detects gene and exon-level deletions and duplications.[14]

Routine whole exome may miss triplet repeat disease. In addition, it can miss exon-level deletions and duplications, microdeletions and duplications, aneuploidy, translocations, inversions, and ring chromosomes (see Box 13.3).[14,16,17] Whole exome studies only sequence protein-coding portions of the genome, and gene coverage varies by laboratory.[18] Some whole exome tests do not sequence mtDNA.

### *Box 13.3* GENETIC CONDITIONS THAT MAY BE MISSED BY ROUTINE WHOLE EXOME

- Deletion or duplication of exons
- Trinucleotide repeats
- Microdeletions or duplications
- Aneuploidy
- Translocations
- Inversions
- Ring chromosomes
- Abnormalities arising from non-protein-coding regions of the genome

**27. A**

Nemaline myopathy is an example of genetic heterogeneity. Most often, it is caused by mutations in the *NEB1* or *ACTA1* genes, but mutations in multiple other genes can also cause this disease.

If a genetic mutation causes variable phenotypes, the term phenotypic pleiotropy is used. Mutations in *ACTA1*, which encodes α-skeletal actin (also known as skeletal muscle α-actin), can cause multiple types of congenital myopathy.[19] Mutations in *ATP1A3* cause multiple phenotypes, including rapid-onset dystonia–parkinsonism (DYT12), alternating hemiplegia of childhood 2, an epileptic encephalopathy, and CAPOS syndrome (cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss).

Mosaicism refers to the presence of cells with different genetic material than the patient's other cells.

X-inactivation, which is also known as lyonization, refers to the normal process in which one of the X chromosomes in cells is silenced during embryogenesis. It is a random process; either the X chromosome from the mother or the X chromosome from the father may be affected. The inactivated X chromosome is referred to as a Barr body.

**28. D**

Nusinersen is an intrathecal treatment for spinal muscular atrophy (SMA), which is due to deficiency of survival motor neuron protein. Nusinersen is an *SMN-2* directed antisense oligonucleotide.

SMA is usually due to mutations in *SMN1*, which encodes survival motor neuron protein. *SMN2* also encodes survival motor neuron protein, but it produces less functional protein than *SMN1*. Nusinersin increases production of full-length survival motor neuron protein. Specifically, it increases exon 7 inclusion in *SMN2* messenger ribonucleic acid (mRNA) transcripts. There is a risk for renal toxicity (including fatal glomerulonephritis), thrombocytopenia, and coagulation abnormalities.[20]

Similar to nusinersen, risdiplam increases exon 7 inclusion in *SMN2* mRNA transcripts and production of full-length survival motor neuron protein.[21] However, risdiplam is an oral solution rather than an intrathecal treatment and has a different mechanism of action. Risdiplam is a survival of motor neuron 2–directed RNA splicing modifier.[21]

Onasemnogene abeparovec-xioi is also a treatment for SMA. It is an intravenous adeno-associated virus vector–based gene therapy that delivers an *SMN1* gene to the motor neurons. There is a risk for liver failure.[22]

**29. B**

Eteplirsen is an antisense oligonucleotide that is "indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping."[23] The most common side effects mentioned in the package insert are balance disorder and vomiting.[23]

Cerliponase alfa is an enzyme replacement therapy used to treat neuronal ceroid lipofuscinosis type 2 (tripeptidyl peptidase 1 deficiency).

Omaveloxolone is a treatment for Friedreich ataxia. It can cause lipid profile abnormalities as well as elevated liver function tests and B-type natriuretic peptide (a marker of cardiac function). Omaveloxolone is an activator of the nuclear factor (erythroid-derived 2)–like 2 (Nrf2) pathway, which is involved in the cellular response to oxidative stress.[24]

Trofinetide, which is an analog of glycine–proline–glutamate (the N-terminal tripeptide of insulin-like growth factor 1), is a treatment for Rett syndrome. Diarrhea is a common side effect.[25,26]

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# 14.

# NEUROINFECTIOUS DISEASES

## QUESTIONS

**1. Match the microscopic appearance with the bacterial species it describes.**

1) Gram-positive coccus
2) Gram-positive bacillus
3) Gram-negative diplococcus
4) Gram-negative coccobacillus
5) Gram-negative bacillus

A. *Streptococcus pneumoniae*
B. *Neisseria meningitidis*
C. *Haemophilus influenzae*
D. *Listeria monocytogenes*
E. *Klebsiella pneumoniae*

**2. What is the most common cause of bacterial meningitis in newborns?**

A. *Haemophilus influenzae*
B. *Neisseria meningitidis*
C. *Streptococcus agalactiae* (group B *Streptococcus*)
D. *Streptococcus pneumoniae*

**3. What is the most common cause of bacterial meningitis in infants, younger children, and adults?**

A. *Haemophilus influenzae*
B. *Neisseria meningitidis*
C. *Staphylococcus aureus*
D. *Streptococcus pneumoniae*

**4. What is the most common cause of bacterial meningitis in teenagers?**

A. *Haemophilus influenzae*
B. *Neisseria meningitidis*
C. *Staphylococcus aureus*
D. *Streptococcus pneumoniae*

**5. A 24-year-old nurse is exposed to meningococcal meningitis in the emergency department. What is the recommended treatment?**

A. Ethambutol
B. Rifampin
C. Streptomycin
D. Isoniazid

**6. Which medications are used for empiric treatment of bacterial meningitis in patients younger than age 50 years who are otherwise healthy?**

A. A second-generation cephalosporin and vancomycin
B. Dexamethasone, a third-generation cephalosporin, and vancomycin
C. Ceftriaxone alone
D. Ampicillin and ceftriaxone

**7. Which of the following statements is *false*?**

A. Chronic meningitis is meningitis lasting longer than 4 weeks.
B. Fever is the most common clinical finding in acute meningitis.
C. Some patients with meningitis need empiric treatment with vancomycin, ceftriaxone, ampicillin, dexamethasone, and acyclovir.
D. Significantly elevated C-reactive protein and procalcitonin levels are more suggestive of viral meningitis than bacterial meningitis.

**8. Which of the following medications is added for coverage of anaerobic bacteria in patients who have otitis, sinusitis, or mastoiditis and suspected meningitis?**

A. Ampicillin
B. Doxycycline
C. Linezolid
D. Metronidazole

**9. True or false?**

It is recommended that tube 1 from a lumbar puncture *not* be sent for Gram stain and culture.

**10. Patients with defects in cell-mediated immunity are at increased risk for meningitis caused by which of the following organisms?**

A. Enterobacteriaceae
B. *Listeria monocytogenes*
C. *Neisseria meningitidis*
D. *Streptococcus pneumoniae*

**11. What is the most common cause of bacterial meningitis in patients who underwent ventriculoperitoneal shunt placement recently?**

A. *Corynebacterium* species
B. *Pseudomonas aeruginosa*
C. *Staphylococcus* species
D. *Streptococcus pneumoniae*

**12. In the treatment of meningitis, ampicillin is added to antibiotic regimens to treat which of the following organisms?**

A. *Escherichia coli*
B. *Haemophilus influenzae*
C. *Klebsiella pneumoniae*
D. *Listeria monocytogenes*

**13. What is the most common cause of viral meningitis?**

A. Enterovirus
B. Herpes simplex virus (HSV)

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C. Cytomegalovirus (CMV)
D. Epstein–Barr virus (EBV)

**14. What is the most common cause of viral encephalitis?**

A. Enterovirus
B. HSV
C. CMV
D. EBV

**15. A 20-year-old man presents with a 2-day history of headache, fever, and worsening confusion. In the emergency department, he has a focal seizure characterized by left-sided clonic activity of the face, arm, and leg. Cerebrospinal fluid (CSF) analysis shows 300 red blood cells (RBCs), 120 white blood cells (WBCs; 85% lymphocytes), glucose 60 mg/dL, and protein 100 mg/dL. CSF Gram staining is negative. Besides magnetic resonance imaging (MRI) of the brain, which test would be the most helpful in diagnosing this condition?**

A. Electroencephalography (EEG)
B. Single-photon emission computed tomography
C. Positron emission tomography
D. Magnetic resonance angiogram

**16. A patient presenting shortly after onset of symptoms is thought to have HSV encephalitis. However, polymerase chain reaction (PCR) analysis of the CSF is negative. What is the next step?**

A. Continue acyclovir and repeat the lumbar puncture.
B. Discontinue acyclovir to prevent renal toxicity.
C. Repeat the PCR on the same sample.
D. Send CSF to an outside laboratory to verify that the PCR is negative.

**17. Which of the following symptoms is most commonly seen in patients with brain abscess?**

A. Altered mental status
B. Headache
C. Fever
D. Seizure

**18. Which of the following conditions is *least* likely to be associated with a brain abscess?**

A. Dental infection
B. Endocarditis
C. Osler–Weber–Rendu disease
D. Stroke
E. Lung infection

**19. A 70-year-old man with poorly controlled diabetes presents with fever and altered mental status. His blood sugar is 450 mg/dL. Urinalysis shows no ketones. CSF analysis shows 0 RBCs, 300 WBCs, glucose 90 mg/dL, and protein 130 mg/dL. What is most likely diagnosis?**

A. Nonketotic hyperosmolar coma
B. Diabetic ketoacidosis
C. Bacterial meningitis
D. Viral meningitis

**20. Which of the following diseases produces a central nervous system (CNS) toxin?**

A. Diphtheria
B. Shigellosis
C. Tetanus
D. All of the above

**21. True or false?**

The presence of immunoglobulin G (IgG) to a bacteria or virus in the CSF proves that the organism is the cause of the CNS infection.

**22. A 20-year-old man presents with fever, headache, malaise, vomiting, and left leg weakness. On examination, his left leg is flaccid and areflexic. Spine MRI showed longitudinally extensive transverse myelitis. Sensation is intact. What is the most likely causative organism?**

A. CMV
B. Salmonella
C. Shigella
D. West Nile virus

**23. What is the most sensitive test for diagnosing West Nile encephalitis?**

A. CSF PCR
B. Measurement of IgM antibodies in the CSF
C. CSF viral culture

**24. Which of the following viruses can cause tremor, myoclonus, parkinsonism, a poliomyelitis-like illness, and encephalitis?**

A. EBV
B. Enterovirus
C. HSV-1
D. West Nile virus

**25. A newborn develops seizures. Head computed tomography (CT) shows periventricular calcifications. What is the most likely diagnosis?**

A. Congenital CMV infection
B. Congenital toxoplasmosis
C. Congenital syphilis
D. Congenital rubella

**26. Lymphocytic choriomeningitis virus is transmitted from which infected animals?**

A. Birds
B. Cats
C. Rodents
D. Lizards

**27. A 50-year-old woman presents with a blistering rash on her trunk and complains of pain and tingling in the area. What is the most likely diagnosis?**

A. Recurrence of a latent varicella-zoster virus
B. CMV polyradiculopathy
C. HSV-1 infection
D. HSV-2 infection

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**28. A 5-year-old unimmunized boy presented with truncal ataxia after developing a vesicles on the trunk and extremities. Of the following viruses, which is most likely to be responsible for his condition?**

A. Measles
B. Rubella
C. Varicella
D. Mumps

**29. Which of the following is the most commonly seen as a neurological complication in mumps infection?**

A. Encephalitis
B. Aseptic meningitis
C. Sensorineural hearing loss
D. Labyrinthitis

**30. Subacute sclerosing panencephalitis (SSPE) is the name for a chronic infection with which of the following viruses?**

A. Measles
B. Mumps
C. Rubella
D. Varicella

**31. Which of the following is most suggestive of an acute EBV infection?**

A. IgM to the EBV viral capsid antigen (VCA)
B. IgG to the EBV VCA
C. IgM to Epstein–Barr nuclear antigen (EBNA)
D. IgG to EBNA

**32. A 30-year-old man with HIV infection presents with chronic headache, confusion, and fever. On examination, there is mild nuchal rigidity. Lumbar puncture shows an elevated opening pressure, 8 RBCs, 175 WBCs with a lymphocytic predominance, a glucose level of 35 mg/dL, and a protein level of 100 mg/dL. Gram staining is negative. India ink staining reveals encapsulated fungi. What is the most likely diagnosis?**

A. Aspergillosis
B. Cryptococcosis
C. Coccidioidomycosis
D. Histoplasmosis

**33. A 65-year-old man with renal failure develops meningitis. After his death, an autopsy is performed. He has thickened leptomeninges and soap bubble-like lesions in the basal ganglia. Which of the following infections is most likely?**

A. Aspergillosis
B. Cryptococcosis
C. Coccidioidomycosis
D. Histoplasmosis

**34. CSF eosinophilic pleocytosis is most suggestive of which of the following infections?**

A. Aspergillosis
B. Blastomycosis
C. Cryptococcosis
D. Coccidioidomycosis
E. Histoplasmosis

**35. Which of the following infections is most likely to occur in patients with poorly controlled diabetes and to cause black nasal mucosa?**

A. Blastomycosis
B. Coccidioidomycosis
C. Histoplasmosis
D. Mucormycosis

**36. A renal transplant recipient returns from the Mississippi River Valley with weight loss, splenomegaly, anemia, fever, and altered mental status. He dies from the illness. On autopsy, he is found to have diffuse meningitis with necrotizing granulomatous inflammation. Organisms resembling small dots are found in the cytoplasm of macrophages. Which of the following infections is most likely?**

A. Aspergillosis
B. Coccidioidomycosis
C. Histoplasmosis
D. Mucormycosis

**37. Which of the following statements is *false*?**

A. Tuberculomas can resemble posterior fossa tumors.
B. Tuberculosis (TB) can be associated with plasma cells in the CSF.
C. TB can cause stroke.
D. TB usually causes noncaseating granulomas.
E. TB can cause cranial nerve palsies and hydrocephalus.

**38. A patient with a history of a pork tapeworm presents with new-onset seizures. Imaging shows multiple parenchymal viable cysts. What is the recommended treatment?**

A. Albendazole, praziquantel, and corticosteroid
B. Doxycycline
C. Pyrimethamine
D. Everolimus

**39. What is the most common neurologic presentation of neurocysticercosis?**

A. Seizure
B. Headache
C. Hemiplegia
D. Hearing loss

**40. Which of the following statements is *false* regarding neurocysticercosis?**

A. Neurocysticercosis is the most common helminthic infection involving the CNS.
B. MRI may miss some cases of neurocysticercosis; patients can have brain parenchymal calcifications alone, which are missed on MRI but seen on CT.
C. A patient with only calcifications does not need to be treated with cysticidal medications.
D. The serum enzyme-linked immunosorbent assay (ELISA) for neurocysticercosis is both very sensitive and very specific.

E. A fundoscopic examination is recommended prior to antiparasitic treatment.

**41. An 18-year-old patient presents with fever, headache, confusion, and rash after a recent hiking trip. The rash started as macules at his wrists and ankles but now involves his trunk, face, palms, and soles. CSF shows a mild pleocytosis. What is the best treatment?**

A. Augmentin
B. Doxycycline
C. Erythromycin
D. Ceftriaxone

**42. Which of the following statements is true regarding toxoplasmosis?**

A. A brain lesion thought to be toxoplasmosis should be biopsied before treatment is begun.
B. A negative CSF PCR result for toxoplasmosis excludes the diagnosis.
C. Toxoplasmosis is the most common cause of ring-enhancing lesions in the brain of patients with AIDS.
D. Lack of antibodies to toxoplasmosis excludes the diagnosis.

**43. Which of the following viruses is linked to primary CNS lymphoma (PCNSL) along with immunosuppression (e.g. AIDS or post-transplant)?**

A. Hepatitis B virus
B. Human papillomavirus
C. CMV
D. EBV

**44. Which of the following statements is *false* regarding neurosyphilis?**

A. Neurosyphilis can cause Heubner arteritis, leading to stroke.
B. When neurosyphilis involves the spinal cord, it is most often associated with degeneration of the anterior horn cells.
C. Neurosyphilis is associated with microglial proliferation in the cortex and iron deposition.
D. Plasma cells may be present in the CSF of patients with neurosyphilis.

**45. Which of the following is *not* associated with congenital syphilis?**

A. Rhinorrhea
B. Hutchinson's teeth
C. Macrocephaly
D. Interstitial keratitis

**46. Poliovirus has the greatest affinity for which type of cell?**

A. Cells in the dorsal root ganglion
B. Cells in the pons
C. Cells in the intermediolateral column
D. Large motor cells in the ventral horn

**47. A 15-month-old boy was brought to the office for evaluation of rash. The boy had a brief generalized tonic–clonic seizure in the setting of high fever 3 days prior. The fever resolved, and then a blanching maculopapular rash appeared on his trunk and extremities. Otherwise, he is alert with good appearance. Which of the following is the most likely cause of this illness?**

A. CMV
B. EBV
C. Human herpes virus type 6 (HHV-6)
D. Rubella

**48. Which of the following organisms infects the CNS via fast retrograde axonal transport from muscle and is associated with intracytoplasmic intraneuronal inclusions?**

A. CMV
B. HIV
C. Rabies virus
D. *Bartonella*

**49. Which cranial nerve is most commonly affected by Lyme disease?**

A. Optic nerve
B. Oculomotor nerve
C. Abducens nerve
D. Facial nerve

**50. Which of the following statements is *false* regarding Lyme disease?**

A. Doxycycline is the preferred treatment for post-treatment Lyme disease syndrome.
B. Doxycycline is the preferred oral treatment for cranial neuropathy associated with Lyme disease.
C. Encephalomyelitis and encephalopathy due to Lyme disease should be treated with parenteral antibiotics.
D. Ceftriaxone, penicillin G, or cefotaxime may be used to treat Lyme disease when parenteral treatment is indicated.

**51. A 24-year-old man with HIV infection who is taking highly active antiretroviral therapy develops focal seizures. Which anti-epileptic medication should be started?**

A. Levetiracetam
B. Carbamazepine
C. Phenytoin
D. Valproic acid

**52. True or false?**

JC virus and herpes virus can be found in normal brains.

**53. Which of the following diseases is associated with demyelination at the juxtacortical white matter, enlarged oligodendrocytes containing virions, and bizarre astrocytes?**

A. EBV infection
B. HIV infection
C. Progressive multifocal leukoencephalopathy (PML)
D. West Nile virus infection

**54. True or false?**

CSF findings (cell count, protein, and glucose) are typically normal in patients with PML.

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**55. Which type of inflammation is found in patients with prion infections?**

A. Eosinophils
B. Lymphocytes
C. Polymorphonuclear lymphocytes
D. Multinucleated giant cells
E. None of the above

**56. Which of the following features is more characteristic of variant Creutzfeldt–Jakob disease (vCJD) than of sporadic CJD?**

A. Florid plaques
B. Increased signal in the basal ganglia and/or cortical ribbon
C. Periodic sharp wave complexes on EEG
D. Shorter clinical course

**57. Which of the following viruses causes T-cell leukemia and tropical spastic paraparesis?**

A. CMV
B. EBV
C. HIV
D. Human T-cell lymphotropic virus-1 (HTLV-1)

**58. Which of the following cranial nerves is most frequently affected by leprosy?**

A. Optic nerve
B. Oculomotor nerve
C. Facial nerve
D. Hypoglossal nerve

**59. Which of the following may develop before the onset of other symptoms in association with COVID-19 infection?**

A. Anomia
B. Anosmia
C. Anarthria
D. Anarithmia

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# NEUROINFECTIOUS DISEASES

## ANSWERS

**1.**

1) A
2) D
3) B
4) C
5) E

See Table 14.1, which provides a list of selected organisms and their descriptions.

*Escherichia coli* and *P. aeruginosa* are also gram-negative bacilli.

*Table 14.1* **MICROSCOPIC APPEARANCE OF SELECTED ORGANISMS**

| ORGANISM | DESCRIPTION |
|---|---|
| *Streptococcus pneumoniae* | **Gram-positive coccus** |
| *Listeria monocytogenes* | **Gram-positive bacillus** |
| *Neisseria meningitis* | **Gram-negative diplococcus** |
| *Haemophilus influenzae* | **Gram-negative coccobacillus** |
| *Klebsiella pneumoniae* | **Gram-negative bacillus** |

**2. C**

Group B streptococcus (*S. agalactiae*) is the most common cause of neonatal meningitis. *Escherichia coli* is the second most common cause.

**3. D**

The most common cause of bacterial meningitis in infants, younger children, and adults is *S. pneumoniae*.

It is recommended that dexamethasone be added to the treatment of pneumococcal meningitis in adults. Due to antibiotic resistance, it is also recommended that these patients have a repeat lumbar puncture 48 hours after initiation of antibiotic therapy.

**4. B**

The most common cause of bacterial meningitis in teenagers is *N. meningitidis*. *Pneumococcal meningitis* is the second most common cause in this age group.

Meningococcal diseases are highly contagious, characterized by high mortality and morbidity, and can occur as an epidemic in military bases or student dormitories. The quadrivalent meningococcal vaccine does not contain serogroup B, so it does not completely prevent meningococcal diseases. Therefore, even if vaccinated, antibiotic prophylaxis is recommended for close contacts with a person with meningococcal diseases.

**5. B**

Medical personnel exposed to meningococcal meningitis should be treated with rifampin.

Patients with asplenia, immunoglobulin deficiency, or defects in the terminal common complement pathway (C3, C5–C9) are at increased risk for *N. meningitidis* and *S. pneumoniae* infection.

Meningococcemia is more likely to cause a rash involving the trunk and lower extremities than most viral causes of meningitis. The rash is petechial. Mucous membranes and conjunctiva may be involved. Viral exanthemas tend to involve the face and chest initially.

**6. B**

Dexamethasone, a third-generation cephalosporin, and vancomycin are recommended for empiric treatment of bacterial meningitis. Blood cultures should be performed before antibiotics are administered.

Ampicillin is added to cover *Listeria* in patients older than age 55 years and in those with decreased cell-mediated immunity.

Doxycycline is added if tick-borne illness is a possibility.

In neurosurgical patients, empiric therapy with vancomycin plus meropenem or ceftazidime is recommended for better gram-negative coverage.

**7. D**

Although fever, neck stiffness, altered mental status, and headache are classically associated with acute meningitis, they may not all be present. Fever is the sign most likely to be present. If there is altered level of consciousness, the patient is more likely to have bacterial meningitis than viral meningitis. Likewise, seizures and focal neurologic deficits are more common in patients with bacterial meningitis. Otitis media, sinusitis, or upper respiratory tract infection symptoms may precede bacterial meningitis.

Significantly elevated levels of C-reactive protein and procalcitonin are more suggestive of bacterial meningitis than viral meningitis (see Box 14.1).

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### *Box 14.1* POTENTIAL COMPLICATIONS DUE TO INFLAMMATION IN MENINGITIS

- Cerebral edema
- Arteritis and infarctions (ischemic and hemorrhagic)
- Hydrocephalus (obstructive and communicating)
- Seizures
- Venous sinus thrombosis

**8. D**

If patients have otitis media, mastoiditis, or sinusitis and meningitis is suspected, metronidazole should be added. Metronidazole is also added for head trauma and for neurosurgical patients. For instance, it is used for anaerobe coverage in patients undergoing ventriculostomy.

Linezolid helps treat *S. epidermidis* and *S. aureus*.

Doxycycline is added for coverage of tick-borne bacterial infections.

Meropenem and ceftazidime cover gram-negative rods that cause nosocomial meningitis, such as *P. aeruginosa*, *E. coli*, and *K. pneumoniae*.

**9. True**

Due to the risk of contamination from skin flora (e.g., coagulase-negative *Staphylococcus*), it is recommended that tube 1 from a lumbar puncture not be sent for Gram stain and culture.

**10. B**

Women in the third trimester of pregnancy and patients with defective cell-mediated immunity (e.g., patients after organ transplant) are at increased risk for *L. monocytogenes* infection. As with group B *Streptococcus*, there is risk for maternal–fetal transmission of *Listeria*. Food-borne *Listeria* can cause outbreaks of listeriosis. The organism can be found in raw meat, raw milk, soft cheeses, and salads. *Listeria* grows in cold (refrigerator) temperatures. Pregnant women should avoid eating cold cuts unless they are heated first.

Patients with defects in the terminal common complement pathway, immunoglobulin deficiency, or asplenia are at increased risk for meningitis from *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* type b.

**11. C**

Coagulase-negative staphylococci and *S. aureus* are the most common organisms isolated from shunt infections.

**12. D**

*Listeria* is particularly a concern in patients older than age 55 years and in patients with decreased cell-mediated immunity, such as those with hematologic malignancies, cancer, or HIV infection; organ transplant recipients; patients who chronically use corticosteroids; and pregnant women.

Ampicillin with or without an aminoglycoside (e.g., gentamycin) remains the first-line drug choice for patients with *Listeria* meningitis.

**13. A**

Enterovirus is the most common cause of viral meningitis.

**14. B**

HSV is the most common cause of viral encephalitis.

In immunosuppressed patients with viral encephalitis, HSV, varicella-zoster virus (VZV), HHV-6, CMV, and EBV need to be considered. Clues that EBV is responsible are a sore throat, tonsillar enlargement, and lymphadenopathy.

**15. A**

This patient has HSV encephalitis and should be treated with acyclovir. HSV encephalitis is characterized by a triad of headache, fever, and altered mental status. Focal seizures and focal neurological defects may be present, including aphasia or hemiparesis. CSF findings may reveal a lymphocytic pleocytosis, elevated protein, as well as elevated RBCs and xanthochromia, reflecting its hemorrhagic nature. HSV encephalitis is associated with lateralized periodic discharges (LPDs) on the EEG. In general, the most common cause of LPDs is stroke.

**16. A**

The CSF PCR for herpes may be negative in the first 72 hours after symptom onset, so a spinal tap should be repeated and a second sample should be sent for PCR testing in this situation. Antibodies to HSV in the CSF may also be helpful. These can be detected in the second week after the onset of symptoms. IgM, IgG, and IgA antibodies to the *N*-methyl-D-aspartate (NMDA) receptor have been found in patients with HSV encephalitis.[1]

CSF IgM antibodies are also helpful in the diagnosis of VZV encephalitis. VZV encephalitis causes demyelinating lesions and infarctions. VZV infects blood vessel endothelial cells and causes vasculitis. It is a cause of focal cerebral arteriopathy.

**17. B**

Headache is observed in the majority of patients with brain abscess. The complete triad of headache, fever, and focal neurologic deficits is present in a minority of cases.

**18. D**

Lung abscesses and endocarditis are risk factors for brain abscesses. Osler–Weber–Rendu disease, also known as hereditary hemorrhagic telangiectasia, is associated with pulmonary arteriovenous malformations, which increase the risk for brain abscesses.

Brain abscesses can also occur with local spread, such as from dental infections, otitis media, sinusitis, or trauma.

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**19. C**

CSF glucose is affected by the blood glucose. CSF glucose is typically approximately two-thirds of blood glucose. In this case, CSF glucose is much lower than expected. CSF protein is also elevated. Therefore, bacterial meningitis is strongly suspected.

**20. D**

Diphtheria, shigellosis, and tetanus all produce CNS toxins.

Shiga toxins produced by *Shigella dysenteriae* can cause altered mental status and seizures.

Tetanus is a paralytic disease. The toxin can cause trismus, muscle spasms and stiffness involving the jaw and neck ("locked jaw"), and opisthotonos. One of the most common forms worldwide is neonatal tetanus. It is still seen in underdeveloped countries; it usually transmits from an unvaccinated mother due to inadequate umbilical stump care.

Diphtheria toxin causes a palatal neuropathy and can cause a demyelinating polyneuropathy resembling Guillain–Barré syndrome.

**21. False**

IgG can be passively transferred to the CSF from the serum. The presence of IgM to an organism in the CSF indicates that the organism is responsible for the infection because IgM antibodies cannot be transferred across the blood–brain barrier. Their presence therefore indicates intrathecal production of antibodies. An elevated antibody index (i.e., the ratio of IgG to an organism in the CSF vs. the serum compared to the ratio of the total IgG in the CSF vs. the serum) can be helpful in determining whether there is intrathecal production of IgG.

**22. D**

This patient has West Nile myelitis. West Nile virus can cause a poliomyelitis-like syndrome (acute flaccid paralysis). Non-polio enteroviruses can as well.

**23. B**

CSF IgM antibodies are most sensitive for diagnosing West Nile encephalitis.

**24. D**

West Nile virus can cause myoclonus, parkinsonism, a polio-like illness, and encephalitis. Gastrointestinal symptoms may also be present in patients with West Nile virus infection.

Other flaviviruses, such as St. Louis encephalitis virus and Japanese encephalitis virus, can also cause encephalitis with parkinsonism. They can infect the basal ganglia, thalamus, and substantia nigra.

**25. A**

CMV is the most common congenital infection. The fetus is typically infected during maternal primary infection. Often, the neonate is asymptomatic. Some patients present later with delayed speech due to hearing loss. CMV is the most common cause of acquired hearing loss in children. Neonates who are symptomatic may have meningoencephalitis, periventricular calcifications, microcephaly, migrational disturbances, or cerebellar hypoplasia. Non-neurologic complications present at birth include hepatitis with hyperbilirubinemia, thrombocytopenia, and coagulopathy.

*Toxoplasma gondii* causes congenital toxoplasmosis. Calcifications can be seen with toxoplasmosis, but they tend to be diffuse rather than limited to the periventricular area.

Symptoms of congenital syphilis include meningitis, mucocutaneous lesions, rashes, hepatosplenomegaly, lymphadenopathy, anemia, osteochondritis, and periostitis. Symptoms may not appear until 2 weeks after birth.

Congenital rubella is associated with intrauterine growth retardation, meningoencephalitis, chorioretinitis and cataracts, cardiovascular anomalies, hepatosplenomegaly, thrombocytopenia with or without purpura, bony radiolucencies, and dermal erythropoiesis.

**26. C**

Lymphocytic choriomeningitis virus (LCMV) is a cause of aseptic meningitis. It results from exposure to infected rodents (hamsters or mice). Also, LCMV is a significant fetal teratogen. Congenital LCMV mimics congenital toxoplasmosis or CMV infection. Congenital LCMV infection should be included in the differential diagnosis for neonates with unexplained ventriculomegaly, hydrocephalus, chorioretinitis, intracranial calcifications, and neurodevelopmental abnormalities.

**27. A**

This is herpes zoster (shingles), which is caused by reactivation of latent varicella-zoster virus (VZV). Both herpes simplex and VZV remain latent in sensory ganglia.

CMV polyradiculopathy can be seen in patients with HIV infection.

HSV-2 is typically sexually transmitted.

**28. C**

Acute cerebellar ataxia is the most common neurological complication of varicella. Acute cerebellar ataxia may occur days to weeks after the onset of varicella-zoster virus infection in children. It is postulated that it may result from an immune-mediated mechanism and the direct invasion of the virus. It typically self-resolves.

**29. B**

CNS involvement is the most common extrasalivary complication of mumps. Aseptic meningitis is the most common neurological complication in mumps. Before the MMR vaccine was introduced, mumps was a common cause of viral meningitis.

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**30. A**

Subacute sclerosing panencephalitis (SSPE) is a degenerative disease that is seen in children and young adolescents who had measles at a young age. First, there is a change in personality and school performance. Then patients develop myoclonus, ataxia, and seizures, followed by rigidity and decreased responsiveness. SSPE causes demyelination that begins in the subcortical white matter. The EEG shows a periodic pattern. Discharges recur every 4 to 15 seconds. (In sporadic CJD, periodic discharges are seen every 0.5 to 1 second.) Elevated anti-measles antibody (IgG) in the serum and CSF is used to help diagnose the condition. CSF protein is increased, and oligoclonal bands can be seen.

**31. A**

First, patients have IgM to the EBV VCA. Next, they develop IgG to the VCA. IgG antibodies to EBNA develop after the virus establishes latency. EBNA antibody usually stays positive for life.

**32. B**

This patient has meningitis due to infection by *Cryptococcus neoformans*, which is an encapsulated fungus. The capsule can be visualized with the use of India ink, but measurement of cryptococcal antigen is more sensitive. *Cryptococcus* infection leads to chronic meningitis characterized by an elevated opening pressure, decreased glucose, elevated protein, and a mild pleocytosis. Cryptococcal meningitis is most common in immunocompromised patients but can occur in immunocompetent individuals. *Cryptococcus* is the most common systemic fungal infection in immunocompromised patients with deficient cell-mediated immunity (e.g., HIV infection, organ transplantation).

In general, Grocott-Gomori methenamine silver (GMS) and periodic acid–Schiff (PAS) stains are useful for identifying fungi.

**33. B**

*Cryptococcus neoformans* infection causes soap bubble–like lesions in the basal ganglia.

**34. D**

Coccidioidomycosis causes a CSF eosinophilic pleocytosis. The organism produces a necrotizing granulomatous inflammatory response with spherules. The spherules release endospores that cause inflammation.

Coccidioidomycosis is caused by *Coccidioides immitis*, which is found in soil and dust in the Southwest. It results in a basal meningitis with small nodules. Acute hydrocephalus may occur.

**35. D**

Mucormycosis is an angioinvasive fungus that can cause thrombosis. It has nonseptate hyphae that branch at right angles. It tends to occur in patients with poorly controlled diabetes and in other immunocompromised patients. It can cause black nasal mucosa due to infarction. It spreads from the nose and sinuses to the brain and causes hemorrhagic lesions often involving the base of the frontal lobes or the deep gray nuclei.

Aspergillosis is also angioinvasive and occurs in immunocompromised hosts, but it has acutely branching septate hyphae. It forms fruiting bodies in culture or tissue section if the organism is exposed to air.

**36. C**

*Histoplasma capsulatum* is endemic in the Ohio and Mississippi River valleys. In infected persons, many *Histoplasma* organisms can be seen in the cytoplasm of macrophages. They look like small dots.

**37. D**

Tuberculosis produces caseating granulomas. Caseating granulomas, also referred to as necrotizing granulomas, are named for their gross appearance of central "cheesy" necrosis. In contrast, sarcoidosis is characterized by noncaseating granulomas.

Tuberculosis is the most common mycobacterial infection of the CNS. It tends to cause basilar meningitis, which can lead to cranial nerve palsies and hydrocephalus. The affected basal meninges enhance with gadolinium. Tuberculous meningitis can also involve the Sylvian fissures, surround the spinal cord, and line the ventricles. CSF shows lymphocytic pleocytosis, reduced glucose, and elevated protein.

TB can cause arterial narrowing and stroke.

When TB causes vertebral disease (tuberculous spondylitis), it is called Pott's disease. It results in a gibbus deformity.

Granulomas in TB are composed of caseating necrosis with multinucleate giant cells, lymphocytes, and plasma cells. Granulomas occur along vessels in the meninges and in the parenchyma.

Sarcoidosis produces noncaseating granulomas, can cause hypothalamic dysfunction, often affects the base of the brain, and can produce cranial nerve palsies (see Box 14.2).

*Box 14.2* CAUSES OF GRANULOMAS

- Mycobacteria
- Fungi
- Spirochetes
- Sarcoidosis
- Foreign material

**38. A**

This patient has neurocysticercosis, which is an infection of the CNS caused by ingestion of eggs from the pork tapeworm *Taenia solium*. Common antiparasitic drugs used to treat neurocysticercosis are praziquantel and albendazole, but praziquantel has generally been less effective than albendazole. Treatment with antiparasitic medication can hasten the death of the cysts and induce an inflammatory reaction. For this reason, steroids should be started prior to antiparasitic drugs. In cases of cysticercotic encephalitis, in which there is a strong inflammatory reaction, there is concern that cysticidal drugs could worsen inflammation, leading to increased intracranial pressure.[2]

The Infectious Diseases Society of America (IDSA) recommends treatment with albendazole and praziquantel if there are more than two viable intraparenchymal cysticerci.[3]

**39. A**

Seizure is the most common neurological presentation of neurocysticercosis.

**40. D**

The complement fixation test and serum ELISA used historically are neither sensitive nor specific for neurocysticercosis. Enzyme-linked immunoelectrotransfer blot using partially purified antigenic extracts has much better sensitivity and specificity if two or more lesions are present; however, it may be falsely negative when there is only one cysticercus.

CSF ELISA for anticysticercal antibodies has some usefulness. However, it also can give false-negative and false-positive findings.[2]

**41. B**

This patient has Rocky Mountain spotted fever (RMSF), which is a tickborne illness caused by the bacterium *Rickettsia rickettsii*. Doxycycline is the treatment for RMSF and other tickborne rickettsial diseases. Cases of RMSF are reported under a new category called Spotted Fever Rickettsiosis (SFR). RMSF causes a characteristic rash that begins on the wrists and ankles and spreads to the rest of the body including the palms and soles. RMSF can cause neurological symptoms, such as lethargy, altered mental status, ataxia, and seizures.

Secondary syphilis and meningococcemia also can cause a rash on the palms and soles.

**42. C**

Central toxoplasmosis is the most common cause of ring-enhancing lesions in a patient with AIDS. Multiple lesions are often seen. Toxoplasmosis is caused by the protozoa *T. gondii*. An abscess caused by this organism is referred to as a "gold coin lesion" because of the discoloration from central coagulative or hemorrhagic necrosis. Patients may not have antibodies, and PCR of the spinal fluid may be negative. Lumbar puncture may not be safe if there is a focal mass lesion. If toxoplasmosis is suspected, one can begin with empiric treatment. It is not necessary to biopsy the lesion first. Pyrimethamine and sulfadiazine are often used to treat toxoplasmosis in combination with folinic acid to mitigate hematologic toxicity associated with pyrimethamine.

The second most common cause of a ring-enhancing lesion with AIDS is primary CNS lymphoma. Primary CNS lymphoma can be solitary, whereas CNS toxoplasmosis is often characterized by multiple lesions.

**43. D**

Primary CNS lymphoma (PCNSL) is a subtype of non-Hodgkin's lymphoma originating in the brain, spinal cord, eyes. or leptomeninges. PCNSL is histologically diffuse large B-cell lymphoma in the vast majority of cases. EBV is associated with the development of various malignancies, including PCNSL especially in immunosuppressed patients. EBV causes monoclonal transformation of B lymphocytes, which in turn can result in PCNSL.

**44. B**

Syphilis is caused by the spirochete *Treponema pallidum*. Neurosyphilis has multiple forms, but it begins as meningitis.

Asymptomatic neurosyphilis is diagnosed by lumbar puncture.

Meningeal syphilis can occur at any time but is most common during the first 2 years after inoculation. The patient may have seizures, cranial nerve palsies, or hydrocephalus.

Meningovascular neurosyphilis is characterized by chronic meningitis and stroke. Infarctions occur because of inflammation and fibrosis affecting small arteries (Heubner arteritis). Branches of the middle cerebral artery are most commonly affected.

Paretic neurosyphilis results from chronic meningoencephalitis. It is characterized by dementia, psychiatric disturbances, seizures, tremor, dysarthria, hyperreflexia, and Argyll–Robertson pupils (pupils accommodate but do not react).

Tabetic neurosyphilis, or tabes dorsalis, develops many years after infection. The dorsal nerve roots and dorsal columns are affected. Symptoms and signs include lancinating pains, lower extremity areflexia, loss of vibration and position sense, sensory ataxia, a positive Romberg sign, and urinary incontinence. Charcot joints (neuropathic arthropathy) may develop.

In active neurosyphilis, the CSF shows pleocytosis with lymphocytes and some plasma cells, increased protein, increased gamma globulin with possible oligoclonal bands, normal glucose, and positive findings on serologic tests.

Neurosyphilis is treated with intravenous penicillin. Penicillin treatment may not improve late neurosyphilitic syndromes but usually halts their progression.

**45. C**

Some congenital syphilis may be asymptomatic at birth but may develop manifestations later if untreated. Early

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congenital syphilis may have signs such as rash involving the palms and soles, rhinorrhea, jaundice, hepatosplenomegaly, and pseudoparalysis due to pain associated with local periostitis. Late congenital syphilis (arbitrarily with onset after age 2 years) may present with the classic triad called Hutchinson's triad, including Hutchinson's teeth (notching of central incisors), interstitial keratitis, and eighth nerve deafness.

**46. D**

Poliovirus affects the anterior (ventral) horn cells. It is a classic cause of asymmetric flaccid paralysis. Patients also have fever and chills. CSF results are consistent with infection.

**47. C**

Primary HHV-6 infection causes roseola (sixth disease) in immunocompetent children and is frequently associated with febrile seizures. HHV-6 infection should be considered for the first episode of febrile status epilepticus. Prolonged febrile seizures or febrile status epilepticus are associated with an increased risk of damage to the hippocampi and later temporal lobe epilepsy.[4]

**48. C**

Negri bodies are found in patients with rabies. Rabies is found in all states and is inevitably fatal once clinical signs develop. The common reservoirs of rabies are bats, raccoons, skunks, foxes, coyotes, mongooses, and unimmunized dogs. The incubation period is generally 1 or 2 months after being bitten or scratched by an infected animal. As rabies progresses, the patient may experience neurological symptoms such as altered mental status, delirium, abnormal behavior, hallucinations, and insomnia. Hydrophobia ("fear of water") is pathognomonic for rabies and occurs in approximately half of patients. Patients with rabies may experience involuntary, painful pharyngeal muscle spasms when swallowing water. Post-exposure prophylaxis consists of one dose of rabies immune globulin and a full course of rabies vaccination to prevent rabies.

**49. D**

Lyme disease is caused by *Borrelia burgdorferi*, a spirochete that is transmitted by ticks. An infected tick must be attached for at least 24 hours to transmit the disease. Proper removal of a tick is with forceps. The most common finding in Lyme disease is the characteristic rash. The rash is called erythema migrans, and it resembles a circular target.

Neurologic manifestations of Lyme disease include lymphocytic meningitis, radiculopathy, and cranial neuropathy. Unilateral or bilateral facial nerve palsy can occur in patients with Lyme disease. Other infectious causes of cranial neuropathy include fungal meningitis, HIV, syphilis, and tuberculosis. Sarcoidosis can also cause bilateral facial palsies.

**50. A**

Post-treatment Lyme disease syndrome is characterized by fatigue and joint pain. Antibiotics are not indicated.[5]

**51. A**

Levetiracetam has no drug interactions and should not affect this patient's medications for HIV. All of the others have a potential for interacting with antiretroviral agents.

Caution should be used when prescribing enzyme-inducing anti-seizure medications (ASMs) such as carbamazepine and phenytoin for patients who are using protease inhibitors or nonnucleoside reverse transcriptase inhibitors because these ASMs may reduce their levels and effectiveness. Similar caution should be paid when enzyme-inducing ASMs are prescribed to women taking oral contraceptives.[6]

**52. True**

JC and herpes viruses can be detected in normal brains; these individuals are asymptomatic carriers.

**53. C**

In PML, JC virus infects oligodendrocytes and astrocytes. Most people carry JC virus. PML is caused by reactivation of the virus. It is an opportunistic infection that primarily affects patients with T-cell deficits, such as patients with AIDS or lymphoreticular malignancies. There is no specific treatment for PML in general. Antiretroviral therapy is the treatment for patients with PML due to HIV.

**54. True**

CSF parameters are generally normal in PML. CSF PCR for JC virus may also be negative. Sometimes, brain biopsy is necessary for diagnosis. The virus affects oligodendrocytes, resulting in demyelination. Viral inclusions can be found in the nuclei of oligodendrocytes.

**55. E**

Prions do *not* cause an inflammatory reaction.

Eosinophils are associated with infection by metazoan parasites; lymphocytes are elevated in viral infections; polymorphonuclear leukocytes are prominent in bacterial infections; and multinucleated giant cells are associated with infection by fungi or mycobacteria.

**56. A**

CJD causes dementia, myoclonus, and motor abnormalities. Microscopically, spongiform encephalopathies such as CJD are characterized by spongiform change, loss of neurons, and gliosis.

vCJD is caused by exposure to transmissible bovine spongiform encephalopathy. Patients tend to be younger than in other forms of CJD and to have early psychiatric symptoms. The prion protein (PRNP) genotype is

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129 MM. Hyperintense signal is seen in the pulvinar on diffusion-weighted imaging (DWI). Florid plaques, which consist of spongiform degeneration with an amyloid core, are found in vCJD.

Most cases of sporadic CJD occur in patients who are homozygotes at codon 129. The clinical course is shorter than in patients with vCJD. Periodic sharp wave complexes may be seen on EEG. DWI shows signal changes in the basal ganglia and/or cortical ribbon (see Table 14.2 and Figure 14.1).

*Table 14.2* COMPARISON OF SPORADIC AND VARIANT FORMS OF CREUTZFELDT–JAKOB DISEASE

| SPORADIC CJD | VARIANT CJD |
|---|---|
| **Mean age of onset and death is the 60s.** | **Mean age of onset and death is the 20s.** |
| **No florid plaques** | **Florid plaques** |
| **Increased signal in basal ganglia and/or cortical ribbon** | **Increased signal in pulvinar** |
| **PSWCs on EEG** | **No PSWCs** |
| **Homozygotes at codon 129 (129 MM or 129 VV)** | **129 MM** |

CJD, Creutzfeldt–Jakob disease; EEG, Electroencephalography; PSWCs, periodic sharp wave complexes.

Patients with sporadic CJD may have elevated levels of 14-3-3, tau, P-tau, and neuron-specific enolase in the CSF. The real-time quaking-induced conversion assay, which measures abnormal prion protein ($PrP^{Sc}$), is a newer test for sporadic CJD.

**57. D**

The majority of HTLV-1 carriers remain asymptomatic throughout their lives. However, HTLV-1 causes adult T-cell leukemia/lymphoma and HTLV-1-associated myelopathy, which is also known as tropical spastic paraparesis. HTLV-1 infection is predominantly seen in areas of high endemicity in southern Japan, the Caribbean basin, parts of South America, and equatorial regions.

**58. C**

Leprosy is a chronic granulomatous disease caused by *Mycobacterium leprae*. *Mycobacterium leprae* tends to affect superficial peripheral nerves because it prefers cooler temperature to grow. Leprosy is traditionally classified into two major types, lepromatous and tuberculoid. Lepromatous leprosy is the systemic form of leprosy and occurs in patients with reduced cell-mediated immunity. Tuberculoid leprosy is the stable form of leprosy and occurs in patients with normal cell-mediated immunity. Tuberculoid leprosy is less severe and less contagious. Thickened peripheral nerves are one of the clinical hallmarks. The ulnar nerve is the most commonly involved peripheral nerve. The common peroneal, facial, and trigeminal nerves are also frequently affected.

**59. B**

Anosmia (smell loss) and ageusia (taste loss) are commonly recognized early during COVID-19 infection, even before onset of other symptoms such as fever or cough. Most patients with anosmia or ageusia recover spontaneously within anywhere between a few weeks and a few months, but some patients may take longer to recover.

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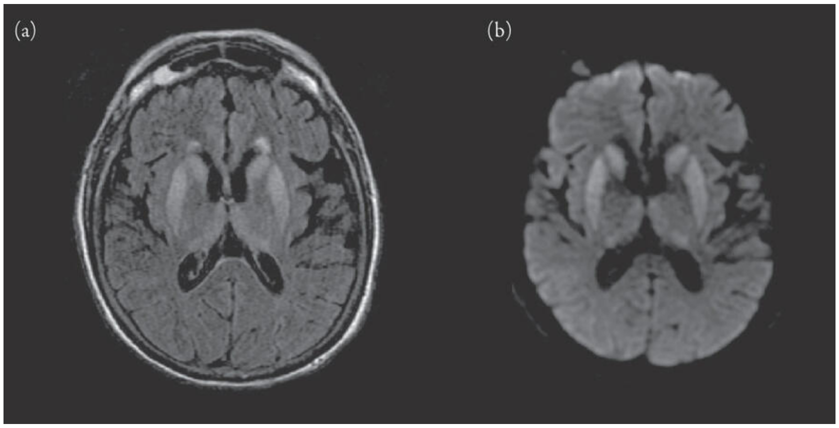

**Figure 14.1** Sporadic Creutzfeldt–Jakob disease. Fluid-attenuated inversion recovery (A) and diffusion-weighted (B) images. SOURCE: From Saba L. *Imaging in Neurodegenerative Disorders*. New York: Oxford University Press; 2015.

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# 15.

# NEUROLOGIC COMPLICATIONS OF SYSTEMIC DISEASES

## QUESTIONS

**1. Which of the following cardiac conditions is most likely to occur in a patient with tuberous sclerosis complex (TSC)?**

A. Aortic regurgitation
B. Mitral valve regurgitation
C. Cardiac rhabdomyomas
D. Hypertrophic cardiomyopathy

**2. A 50-year-old with cirrhosis becomes confused and develops asterixis. What is the classic electroencephalography finding in hepatic encephalopathy?**

A. Alpha coma
B. Beta coma
C. Delta brushes
D. Triphasic waves

**3. Which of the following is *not* a risk factor for dialysis disequilibrium syndrome (DDS)?**

A. First dialysis treatment
B. Low blood urea nitrogen (BUN)
C. Rapid dialysis
D. Hypernatremia

**4. What is the most common neurologic complication of inflammatory bowel disease?**

A. Encephalopathy
B. Myopathy
C. Peripheral neuropathy
D. Stroke

**5. Which of the following is *least* likely to be associated with cardiac complications?**

A. Myotonic dystrophy
B. Friedreich ataxia
C. Puffer fish poisoning
D. Pompe disease

**6. Wilson disease is caused by a defect in which of the following?**

A. A copper-transporting adenosine triphosphatase (ATPase)
B. Ceruloplasmin production
C. Cytochrome *c* oxidase
D. Decreased urinary excretion of copper

**7. A 71-year-old female presented with weight loss, significant constipation, and abdominal distention. Abdominal computed tomography (CT) scan showed residual food in the stomach but no overt obstruction. Gastric emptying scintigraphy was consistent with gastroparesis. If this is paraneoplastic gastroparesis, which of the following cancers is most likely to be found in this patient?**

A. Breast
B. Colon
C. Lung
D. Ovary

**8. Neurologic complications can occur with bariatric surgery. Which of the following is *least* likely to be seen in patients who have undergone bariatric surgery?**

A. Wernicke encephalopathy
B. Myelopathy
C. Polyneuropathy
D. Subarachnoid hemorrhage

**9. Which of the following diseases is most likely to cause fever, diarrhea, parkinsonism, and oculomasticatory myorhythmia?**

A. Celiac disease
B. Crohn disease
C. Ulcerative colitis
D. Whipple disease

**10. A middle-aged patient with Down syndrome, epilepsy, and ataxia underwent a brain CT, which revealed occipital calcifications. Which of the following diagnoses is most likely?**

A. Celiac disease
B. Crohn disease
C. Ulcerative colitis
D. Whipple disease

**11. A 30-year-old pregnant woman develops confusion and new-onset seizure activity. Vital signs show that she is afebrile but hypertensive. She seems to have difficulty focusing on objects. Which of the following findings is most likely to be seen on magnetic resonance imaging (MRI)?**

A. Pituitary hemorrhage
B. Increased T2 signal in both temporal lobes
C. Mesial temporal sclerosis
D. Vasogenic edema in the occipital and parietal lobes bilaterally

**12. An 18-year-old with polycystic kidney disease presents with severe headache, vomiting, and photophobia. Which diagnosis needs to be ruled out?**

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A. Cluster headache
B. Migraine
C. Pituitary apoplexy
D. Subarachnoid hemorrhage

**13. Which cranial nerve is most frequently involved in patients with neurosarcoidosis?**
A. Optic nerve
B. Oculomotor nerve
C. Abducens nerve
D. Facial nerve

**14. Which of the following is the most common neurologic manifestation of polycythemia vera?**
A. Peripheral neuropathy
B. Cerebral infarction
C. Seizure
D. Tremor

**15. A 60-year-old woman with a past medical history of hypertension and hyperlipidemia suffered from acute myocardial infarction. One week after stent angioplasty and starting clopidogrel, she presents with fever, headache, epistaxis, and altered mental status. The patient is found to have thrombocytopenia, microangiopathic hemolytic anemia, and renal impairment (serum creatinine was 2.0 mg/dL). Schistocytes are seen on her peripheral blood smear. What is the most likely diagnosis?**
A. Hemolytic uremic syndrome (HUS)
B. Idiopathic thrombocytopenic purpura (ITP)
C. Disseminated intravascular coagulation
D. Thrombotic thrombocytic purpura (TTP)

**16. Which of the following combinations of vitamin deficiency and illness is *incorrect*?**
A. Vitamin A toxicity – idiopathic intracranial hypertension
B. Vitamin $B_2$ deficiency – pellagra
C. Vitamin E deficiency – cerebellar ataxia
D. Folate – pernicious anemia

**17. Which of the following conditions is *least* likely to be the result of hypothyroidism?**
A. "Hung up" reflex (delayed relaxation)
B. Hypokalemia
C. Muscle cramps
D. Encephalopathy

**18. Which of the following conditions is *least* likely to be a result of hyperthyroidism?**
A. Cerebellar ataxia
B. Myasthenia gravis
C. Chorea
D. Periodic paralysis

**19. In which of the following conditions is pheochromocytoma *least* likely to occur?**
A. Neurofibromatosis type 1
B. Von Hippel-Lindau syndrome (VHL)
C. Tuberous Sclerosis Complex
D. Multiple endocrine neoplasia type 2 (MEN 2)

**20. A 20-year-old woman with central adrenal insufficiency is scheduled for appendectomy. Which medication should be given around the time of surgery?**
A. Hydrocortisone
B. Fludrocortisone
C. Salt tablets
D. Desmopressin

**21. A 20-year-old man is referred to neurology for a pituitary mass that was compressing the visual chiasm on MRI. Which visual defect is most likely to be present?**
A. Bitemporal hemianopsia
B. Binasal hemianopsia
C. Homonymous hemianopsia
D. An enlarged blind spot

**22. A 40-year-old woman underwent total thyroidectomy for thyroid cancer. Shortly after the surgery, the patient began complaining of fatigue, muscle cramps around her mouth, and neurocognitive dysfunction. Laboratory studies showed an elevated level of serum creatine phosphokinase (CPK). What is the most likely diagnosis?**
A. Hypothyroidism
B. Hypoparathyroidism
C. Malignant hyperthermia
D. Serotonin syndrome

**23. Which of the following disorders is *least* likely to be associated with atlanto-axial dislocation?**
A. Trisomy 21
B. Rheumatoid arthritis
C. Thoracic outlet syndrome
D. Marfan syndrome

**24. Purkinje cell antibody 2 (PCA-2), antineuronal nuclear antibody type 2 (ANNA-2), ANNA-3, amphiphysin, and γ-aminobutyric acid (GABA) receptor paraneoplastic antibodies are all associated with which type of cancer?**
A. Breast adenocarcinoma
B. Renal cell carcinoma
C. Small cell lung carcinoma
D. Thymoma

**25. Which of the following syndromes is *not* typically associated with an increased risk for brain tumors?**
A. Turcot syndrome
B. Gorlin syndrome
C. Li–Fraumeni syndrome
D. Peutz–Jeghers syndrome

**26. Which of the following is more likely to involve the brainstem than supratentorial areas?**
A. Primary angiitis of the central nervous system (PACNS)
B. Neuro-Behçet syndrome
C. Herpes simplex encephalitis (HSE)
D. Arteriovenous malformation (AVM)

**27. Patients with chronic hepatitis C are at highest risk for which of the following disorders?**

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A. Cryoglobulinemia
B. Idiopathic thrombocytopenic purpura
C. Waldenstrom macroglobulinemia
D. Monoclonal gammopathy of unknown significance

**28. Which nutritional deficiency is associated with acanthocytosis?**

A. Folate deficiency
B. Vitamin A deficiency
C. Vitamin E deficiency
D. Vitamin K deficiency

**29. A patient with a history of intellectual disability presents to the emergency department with muscle cramps and seizures. On examination, she is petite in height. She has a round face and cataracts. Tetany is elicited. Which of the following is most likely to be present?**

A. Polycystic kidney disease
B. A cherry-red spot
C. Concentric cardiomyopathy
D. Shortening of the metacarpal and metatarsal bones

**30. Which of the following is a medium-vessel vasculitis?**

A. Giant cell arteritis
B. Immunoglobulin A (IgA) vasculitis
C. Takayasu arteritis
D. Polyarteritis nodosa

# NEUROLOGIC COMPLICATIONS OF SYSTEMIC DISEASES

## ANSWERS

**1. C**

Cardiac rhabdomyomas are the most common primary tumor of the heart in infants and children. They are highly associated with tuberous sclerosis complex (TSC). Therefore, if cardiac rhabdomyomas are found prenatally, the finding can lead to the prenatal diagnosis of TSC. They may cause no symptoms, but in a minority of cases there may be obstruction of blood flow within the heart.

Wolff–Parkinson–White syndrome can also occur in patients with TSC.

**2. D**

Hepatic encephalopathy manifests with confusion and movement disorders such as asterixis, myoclonus, or tremor. Patients with fulminant liver failure can have increased intracranial pressure. Comatose patients with acute hepatic failure may have cerebral edema, which can be fatal. Grade 4 hepatic failure is associated with dilated pupils, loss of cranial nerve reflexes, posturing, and loss of deep tendon reflexes. An elevated ammonia level is seen in hepatic encephalopathy. Triphasic waves are the classic finding in hepatic encephalopathy, but they are not specific to liver disease.

Wilson disease and Niemann–Pick disease type C are diseases with neurologic manifestations that can also cause hepatic failure.

**3. B**

Dialysis disequilibrium syndrome (DDS) is a neurological disorder caused by rapid clearance of medium molecules from the blood. This leads to a widened osmotic gradient between the blood and cerebrospinal fluid, resulting in brain edema. Symptoms may include nausea, emesis, headache, dizziness, altered mental status, and seizures. DDS occurs during or shortly after dialysis. Risk factors include first and/or rapid dialysis, high BUN, hypernatremia, hyperglycemia, metabolic acidosis, and preexisting neurological abnormalities.

**4. C**

Peripheral neuropathy is the most common neurologic complication of inflammatory bowel disease. The cause is thought to be multifactorial (e.g., nutritional, immune-mediated, and medication-related).

**5. C**

Myotonic dystrophy, Friedreich ataxia, and Pompe disease affect cardiac muscle.

Tetrodotoxin found in pufferfish is one of the most toxic poisons in nature. It blocks voltage-gated sodium channels and can cause respiratory paralysis.

**6. A**

Wilson disease is caused by a defect in a copper-transporting ATPase that results from a mutation in the *ATP7B* gene on chromosome 13. Copper cannot be transported to the bile canaliculus to be excreted, so it accumulates in the liver. Excessive copper is then deposited in other tissues. Tremor is the most common neurologic manifestation. Urinary copper is increased. Serum copper and ceruloplasmin are reduced. Wilson disease is treated with copper chelation.

**7. C**

The most common antibody associated with paraneoplastic gastroparesis is anti-Hu antibody (also known as antineuronal nuclear antibody type 1 [ANNA-1]). It is most commonly found in patients with small-cell lung cancer. Anti-Hu antibody can also cause a sensory neuropathy/neuronopathy and paraneoplastic encephalomyelitis.

**8. D**

Wernicke encephalopathy and polyneuropathy due to vitamin $B_1$ (thiamine) deficiency can occur after bariatric surgery. Myelopathy due to vitamin $B_{12}$ deficiency can develop later. Encephalopathy, myopathy, peripheral neuropathy, and nutritional optic neuropathy are also possible complications of bariatric surgery.

Subarachnoid hemorrhage is not commonly seen in patients who have undergone bariatric surgery.

**9. D**

Oculomasticatory myorhythmia is a pathognomonic neurologic sign of Whipple disease. Whipple disease is caused by the bacterium *Tropheryma whipplei*. It tends to affect middle-aged men. It causes systemic manifestations such as diarrhea, weight loss, fever, abdominal pain, and polyarthritis. Neurologic manifestations include changes in personality, cognitive decline, supranuclear gaze palsy, myoclonus, parkinsonism, and oculomasticatory myorhythmia. Intestinal biopsy aids in the diagnosis; periodic acid–Schiff-positive bacteria are seen within macrophages.

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**10. A**

Celiac disease is an immune-mediated malabsorption syndrome characterized by permanent gluten intolerance. The most common neurological complications are seizures and ataxia. Occipital calcifications can be identified in patients with celiac disease. The combination of celiac disease, epilepsy, and cerebral calcifications is called CEC syndrome. Patients with Down syndrome have increased risk for celiac disease.

**11. D**

This patient has posterior reversible encephalopathy syndrome (PRES), which is also known as reversible posterior leukoencephalopathy. Symptoms include headache, vision changes, seizures, and altered mental status. Typically, vasogenic edema occurs in the occipital and parietal lobes bilaterally. However, signal abnormality may extend more anteriorly and even to the cerebellum, and it may not be fully reversible. Hypertension and preeclampsia/eclampsia are risk factors for PRES. PRES can also occur in sepsis, in transplant recipients, in patients receiving immunosuppressive medications (e.g., cyclosporin or tacrolimus), and in autoimmune disease.

**12. D**

Subarachnoid hemorrhage needs to be ruled out. Patients with polycystic kidney disease are at risk for cerebrovascular malformations such as saccular aneurysms and dolichoectasia. Some patients with TSC have polycystic kidney disease.

Pituitary apoplexy, which is caused by infarction or hemorrhage of the pituitary gland, is another cause of thunderclap headache. In addition to severe headache, the patient may have vision changes, ophthalmoplegia, altered mental status, and hormone dysfunction. Subarachnoid hemorrhage may be present. Risk factors include pituitary macroadenoma and postpartum status. Pituitary apoplexy is treated with hydrocortisone.

**13. D**

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology, characterized by noncaseating granulomas and multinucleated giant cells. Cranial neuropathy is a frequent manifestation of neurosarcoidosis due to basal meningitis. The facial nerve (the seventh cranial nerve) is the most frequently affected cranial nerve, followed by the optic nerve. The presence of bilateral facial palsy with bilateral hilar lymph node enlargement on chest X-ray should raise suspicion for sarcoidosis. The patient may have an elevated concentration of angiotensin-converting enzyme. Hypercalcemia can occur. Conjunctival biopsy can aid in the diagnosis of neurosarcoidosis.

**14. B**

Polycythemia vera is a neoplastic condition in the marrow that causes overproduction of red blood cells. The most common neurologic complications of polycythemia vera are cerebral infarction and transient ischemic attack due to hyperviscosity and impaired cerebral blood flow.

**15. D**

Thrombotic thrombocytopenic purpura (TTP) is a rare disorder that is classically characterized by the pentad of thrombocytopenia, microangiopathic hemolytic anemia, variable neurologic symptoms, fever, and kidney dysfunction. An association between clopidogrel and TTP has been reported.

Hemolytic uremic syndrome (HUS) can also cause microangiopathic hemolytic anemia and thrombocytopenia. It tends to occur in children. Patients with HUS often have a gastrointestinal illness with fever and diarrhea. Then renal failure occurs, resulting in reduced urine output and edema. Anemia and thrombocytopenia cause paleness and petechiae. Neurologic symptoms are less prominent than in TTP, but headache, irritability, lethargy, and seizures can occur in HUS. *Escherichia coli* O157:H7 and *Shigella* infections can cause HUS.

Often, HUS and TTP can be difficult to differentiate clinically. Age helps differentiate the two; HUS is primarily seen in children, whereas TTP is more likely to be seen in adults. Also, renal symptoms are more prominent in HUS, and neurologic symptoms are more prominent in TTP.

Patients with idiopathic thrombocytopenia purpura (ITP) do not have anemia and are less ill-appearing than patients with TTP; however, intracranial hemorrhage can occur in ITP if thrombocytopenia is severe.

**16. B**

Pellagra is a nutritional disorder due to niacin (vitamin $B_3$) deficiency (not vitamin $B_2$ deficiency). Pellagra is associated with the triad of diarrhea, dermatitis, and dementia.

Riboflavin (vitamin $B_2$) deficiency causes glossitis and dryness and cracking of the skin around the lips.

Idiopathic intracranial hypertension is associated with vitamin A toxicity.

Vitamin E deficiency causes cerebellar ataxia.

Folate (vitamin $B_9$) or vitamin $B_{12}$ deficiency causes pernicious anemia (megaloblastic anemia).

**17. B**

Hypothyroidism causes delayed relaxation during reflex testing, muscle cramps, and encephalopathy.

**18. A**

Cerebellar ataxia can occur with hypothyroidism.

The most common movement disorder in hyperthyroidism is tremor. Usually, this is a postural tremor of the hands. It improves with β-blockers. Chorea secondary to hyperthyroidism may also respond to β-blockers.

Hyperthyroidism is associated with several neuromuscular disorders, including periodic paralysis, myasthenia gravis, neuropathy, and myopathy. Thyrotoxic periodic paralysis is associated with hypokalemia and is treated with potassium and nonselective β-blockers.

**19. C**

Pheochromocytoma occurs in neurofibromatosis type 1, Von Hippel-Lindau (VHL) syndrome, and MEN 2. It is rarely seen in tuberous sclerosis complex.

VHL syndrome is caused by mutations in the VHL tumor suppressor gene on chromosome 3. Hemangioblastoma is a common presentation. Patients with VHL syndrome are at risk for cerebellar and spinal cord hemangioblastomas, retinal angiomas, renal cell carcinoma, pheochromocytomas, epididymal cystadenomas, bilateral endolymphatic sac tumors, and kidney and pancreatic cysts.

Pheochromocytoma can be seen in patients with MEN 2A and MEN 2B. Patients with MEN 2 are at risk for medullary carcinoma of the thyroid. Patients with MEN 2A may develop parathyroid disease. Patients with MEN 2B may have a marfanoid habitus and mucosal neuromas. (MEN 1 tends to affect the pituitary, pancreas, and parathyroid glands. Facial angiofibromas, meningioma, and ependymoma can also occur in MEN 1.)

**20. A**

Patients with adrenal insufficiency require stress dosing of steroids when they are ill or undergoing surgery. Glucocorticoids, such as prednisone and hydrocortisone, are typically used for replacement. Fludrocortisone is a mineralocorticoid. Mineralocorticoids are under control of the renin–angiotensin system and do not need replacement if a patient has central adrenal insufficiency.

**21. A**

Pituitary tumors can cause bitemporal hemianopia due to pressure on the optic chiasm.

Pituitary adenomas are a common type of pituitary tumor. They typically arise from the anterior pituitary. Prolactinoma is the most common pituitary adenoma. Bromocriptine, which is a dopamine agonist, can be used to treat prolactinomas. (Dopamine inhibits prolactin secretion.) Dopamine agonists can have psychiatric side effects.

Pituitary tumors that produce growth hormone can cause acromegaly. Neurologic complications of acromegaly include peripheral neuropathy, especially of the median nerve; proximal myopathy; and obstructive and central sleep apnea.

Pituitary tumors can also produce adrenocorticotropic hormone, causing Cushing disease due to hypercortisolism. Patients have truncal obesity, hypertension, abdominal striae, hirsutism, glucose intolerance, and later osteoporosis. Neurologic complications include myopathy, headache, and possible cognitive and psychiatric changes.

Binasal hemianopia can be caused by bilateral calcified internal carotid arteries.

**22. B**

Hypoparathyroidism is one of the common complications after total thyroidectomy and can cause various neurological symptoms related to hypocalcemia. Muscle cramps notably involving facial muscles are very common in patients with hypocalcemia. Laboratory testing also may show hyperphosphatemia and increased CPK.

**23. C**

Altanto-axial subluxation is misalignment of the first and second cervical vertebrae that can potentially lead to fatal spinal cord compression. Atlanto-axial subluxation can be seen in patients with autoimmune disorders (e.g., rheumatoid arthritis), connective tissue disorders (e.g., Marfan syndrome), and some genetic disorders (e.g., trisomy 21).

**24. C**

PCA-2, ANNA-1, ANNA-2, ANNA-3, amphiphysin, and γ-aminobutyric acid (GABA) receptor paraneoplastic antibodies are associated with small cell lung carcinoma.

**25. D**

Peutz–Jeghers syndrome is *not* usually associated with brain tumors. It is associated primarily with gastrointestinal, pancreatic, breast, gynecologic, or lung cancers.

Turcot syndrome is associated with gliomas and medulloblastomas in addition to adenomatous colon polyps and adenocarcinoma.

Gorlin syndrome, or basal cell nevus syndrome, is associated with basal cell carcinomas and medulloblastomas.

Li–Fraumeni syndrome is associated with gliomas and medulloblastomas in addition to breast cancer, sarcomas, and leukemias.

**26. B**

Behçet disease is a multisystem autoimmune disease. It often presents with orogenital ulcers, uveitis, and skin lesions (erythema nodosum and acneiform lesions). Behçet disease can affect multiple areas of the central nervous system and can mimic multiple sclerosis. Neuro-Behçet syndrome most commonly involves the brainstem.

Primary angiitis of the central nervous system (PACNS) and arteriovenous malformations (AVMs) can also be seen anywhere in the brain, brainstem, or spinal cord, but they are most commonly seen in the cerebral hemispheres.

Herpes simplex encephalitis (HSE) primarily affects the medial temporal lobe.

**27. A**

Patients with chronic hepatitis C often have cryoglobulinemia.

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**28. C**

Vitamin E deficiency causes acanthocytosis. Acanthocytosis occurs in abetalipoproteinemia and hypobetalipoproteinemia types I and II.

A group of conditions involving acanthocytosis and neurologic symptoms, especially movement disorders, are called neuroacanthocytoses. Examples are chorea-acanthocytosis (choreoacanthocytosis), Huntington disease-like 2, McLeod syndrome, and pantothenate kinase-associated neurodegeneration (PKAN).

**29. D**

Tetany can occur with hypocalcemia, hypomagnesemia, and respiratory alkalosis (as seen with hyperventilation). This patient has hypocalcemia due to pseudohypoparathyroidism. Specifically, she has Albright hereditary osteodystrophy. These patients can have seizures, tetany, intellectual disability, basal ganglia calcification, and cataracts. Shortening of the metacarpal and metatarsal bones can be seen.

**30. D**

Polyarteritis nodosa affects medium-sized vessels. It can cause neuropathy, including mononeuritis multiplex.

Giant cell arteritis can cause arteritic anterior ischemic optic neuropathy, which requires prompt treatment with steroids to prevent vision loss. Tocilizumab, which is an interleukin-6 inhibitor, has been used as adjunctive treatment for giant cell arteritis.[1]

Small-vessel vasculitis is divided into anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis and immune complex small-vessel vasculitis.

ANCA-associated vasculitis tends to cause granulomatosis. ANCA-associated small-vessel vasculitis includes granulomatosis with polyangiitis (formerly Wegener granulomatosis), eosinophilic granulomatosis with polyangiitis (formerly Churg–Strauss syndrome), and microscopic polyangiitis.

Immune complex systemic vasculitis includes IgA vasculitis (Henoch–Schönlein purpura). Immune complex systemic vasculitis tends to cause leukocytoclastic vasculitis.

Henoch–Schönlein purpura is more common in children than in adults. Headache and behavioral changes can be seen, but significant central nervous system involvement is rare. Henoch–Schönlein purpura manifests with systemic symptoms such as fever and anorexia. There may be an antecedent infection. Then the patient develops a rash (palpable purpura without thrombocytopenia), abdominal pain, and joint pain. Intussusception and glomerulonephritis can occur. The lungs may also be affected.

## REFERENCE

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# 16.

# NEUROMUSCULAR DISEASES

## QUESTIONS

1. **Fill in the blank: The nerves proximal to the formation of the brachial plexus are the ____________________.**
   A. Nerve to the subclavius and lateral pectoral nerve
   B. Suprascapular nerve and nerve to the subclavius
   C. Dorsal scapular nerve and long thoracic nerves
   D. Suprascapular nerve and lateral pectoral nerves

2. **A 30-year-old woman undergoes radical mastectomy. Postoperatively, she has shoulder weakness and scapular winging. Which nerve was injured?**
   A. Axillary nerve
   B. Long thoracic nerve
   C. Subscapular nerve
   D. Thoracodorsal nerve

3. **A lesion of which of the following nerves is most likely to cause wrist drop?**
   A. Anterior interosseous nerve
   B. Median nerve
   C. Radial nerve
   D. Ulnar nerve

4. **Which of the following tests aids in differentiating posterior cord plexopathy from radial neuropathy?**
   A. Test shoulder abduction
   B. Test finger extension
   C. Test elbow extension
   D. Test wrist extension

5. **Which muscle abducts the shoulder through the first 15 degrees?**
   A. Deltoid
   B. Serratus anterior
   C. Supraspinatus
   D. Trapezius

6. **A patient presents with wrist drop, mild weakness of supination and elbow flexion, and sensory loss over the dorsum of the hand. Elbow extension is strong. A radial neuropathy is suspected. Where is the lesion most likely to be located?**
   A. In the axilla
   B. In the spiral groove
   C. Just above the elbow
   D. In the forearm

7. **A 24-year-old transcriptionist presents with wrist pain that is worse in her dominant hand. She has been awakening at night with paresthesias in her hands that improve when she shakes her hands. Tapping a reflex hammer to her wrist reproduces the symptoms. Which of the following is *least* likely to be present in this condition?**
   A. Numbness over the thenar eminence
   B. Weakness of the thenar eminence
   C. Decreased sensation in the first, second, third, and fourth digits with sparing of the medial side of the fourth digit
   D. Paresthesias when the wrist is passively flexed

8. **A lesion at which of the following locations causes ulnar palmar sensory loss and weakness of all the ulnar-innervated intrinsic hand muscles?**
   A. Carpal tunnel
   B. Guyon's canal
   C. Midpalm
   D. Pisohamate hiatus

9. **Which of the following muscles has innervation from the obturator nerve and the tibial division of the sciatic nerve?**
   A. Adductor magnus
   B. Gluteus maximus
   C. Pectineus
   D. Short head of the biceps femoris

10. **An obese patient presents with dysesthesia in the lateral aspect of the upper thigh. Compression of which nerve is most likely responsible?**
    A. Lateral femoral cutaneous nerve
    B. Cutaneous branch of the obturator nerve
    C. Intermediate cutaneous nerve of the thigh
    D. Femoral nerve

11. **A patient presents with pain in the buttock that radiates down the posterior aspect of his leg to the lateral aspect of his foot. He has decreased sensation in a similar distribution. Hip extension, knee flexion, plantar flexion, and toe flexion are weak, and his ankle jerk reflex is decreased. What is the diagnosis?**
    A. L4 radiculopathy
    B. L5 radiculopathy
    C. S1 radiculopathy
    D. Peroneal lesion

12. **What is the most common pattern of muscle weakness in myopathies?**
    A. Distal arm and distal leg weakness
    B. Distal arm and proximal leg weakness
    C. Proximal arm and distal leg weakness
    D. Proximal arm and proximal leg weakness

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**13. Which of the following statements is *false*?**

A. Congenital myopathies tend to manifest with hypotonia and weakness.
B. Congenital myopathies can be evident at birth.
C. Congenital myopathies tend to cause rapidly progressive clinical worsening.
D. Historically, muscle biopsy was used to classify congenital myopathies.

**14. A child is brought to the clinic for developmental delay. He is hypotonic and has proximal muscle weakness. He has a history of hip dislocation and was recently diagnosed with scoliosis. His mother states that the child's brother has similar symptoms and had an adverse reaction to halothane. The patient undergoes a muscle biopsy, which shows absence of mitochondria in the middle of the muscle fibers. What is the most likely diagnosis?**

A. Cap myopathy
B. Central core disease
C. Nemaline rod myopathy
D. Zebra body myopathy

**15. A newborn has a high-arched palate, hypotonia, and weakness. His creatine phosphokinase (CPK) level is slightly elevated. Muscle biopsy shows rods containing α-actinin that are in continuity with the Z lines. What is his diagnosis?**

A. Central core myopathy
B. Nemaline myopathy
C. Myotubular myopathy
D. Congenital muscular dystrophy (CMD)

**16. A mutation in which of the following genes causes merosin-deficient congenital muscular dystrophy (CMD)?**

A. *POMT1*
B. *POMGnT1*
C. *LAMA2*
D. *SEPN1*

**17. True or False?**

Botulinum toxin can cause prolonged weakness in patients with congenital muscular dystrophy (CMD).

**18. Patients with which of the following conditions can have cardiac involvement?**

A. Merosin-deficient CMD
B. Fukuyama CMD
C. Selenoprotein N–related myopathy/CMD with spinal rigidity
D. All of the above

**19. Patients with which CMD may have seizures?**

A. Merosin-deficient CMD
B. Fukuyama CMD
C. Muscle–eye–brain disease
D. All of the above

**20. Which of the following diseases is associated with poor head control early in life, spinal stiffness and progressive restrictive respiratory failure later in life, and desmin-positive inclusions?**

A. α-Dystroglycan–related dystrophies
B. Collagen VI–related myopathies
C. Laminin $\alpha_2$-related CMD
D. Selenoprotein N–related myopathy/CMD with spinal rigidity

**21. A 6-year-old boy presents with falls, toewalking, and difficulty running. His symptoms began at age 3 years. On examination, he has calf hypertrophy, mild lordosis, head lag when pulled to sitting from the supine position, and difficulty arising quickly from the floor. His CPK level is significantly elevated. Which of the following treatments has been proven to improve this condition?**

A. Carnitine
B. Creatine
C. Oral corticosteroids
D. Coenzyme Q10

**22. An 18-year-old competitive softball player presents with difficulty throwing a softball. On examination, she has a transverse smile, widened palpebral fissures, scapular winging, and reversal of the anterior axillary folds. Her deltoids are strong, but her biceps, triceps, and pectoral muscles are weak. She has no contractures. Which of the following is most likely to occur in this condition?**

A. Cardiomyopathy
B. Dysphagia
C. Hearing loss
D. Respiratory insufficiency

**23. A 50-year-old woman presents with difficulty swallowing. On examination, she has ptosis and ophthalmoplegia. She denies double vision. Her mother and sister have similar symptoms. What is the most likely diagnosis?**

A. Mitochondrial myopathy
B. Myotonic dystrophy
C. Fascioscapulohumeral dystrophy
D. Oculopharyngeal dystrophy

**24. Patients with which of the following conditions are most likely to have asymmetric facial muscle weakness?**

A. Fascioscapulohumeral dystrophy
B. Myasthenia gravis (MG)
C. Myotonic dystrophy
D. Oculopharyngeal dystrophy

**25. A 10-year-old boy presents with toe walking. On examination, he has contractures at the elbows and ankles. An electrocardiogram shows first-degree atrioventricular block. The creatine kinase (CK) level is mildly elevated. The patient's older brother had similar symptoms and later developed a rigid spine. A mutation in which of the following genes is most likely the cause?**

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A. *LMNA*
B. *SMN1*
C. *SMN2*
D. *ZNF9*

**26. Which of the following is an autosomal dominant limb–girdle muscular dystrophy (LGMD) that often manifests with myalgia and is associated with rippling muscles and a very high CK level?**
A. LGMD1A/myofibrillar myopathy (myotilinopathy)
B. LGMD1B/Emery–Dreifuss muscular dystrophy (laminopathy)
C. LGMD1C (caveolinopathy)
D. LGMDD1 DNAJB6-related (formerly LGMD1D)
E. LGMD1E/myofibrillar myopathy (desminopathy)

**27. Which of the following is both the most common LGMD and due to an enzyme defect?**
A. LGMDR1 calpain3-related (formerly LGMD2A)
B. LGMDR2 dysferlin-related (formerly LGMD2B)
C. LGMDR5 $\gamma$-sarcoglycan-related (formerly LGMD2C)
D. LGMDR9 FKRP-related (formerly LGMD2I)

**28. Mutations in which of the following genes cause inclusion body myopathy with Paget disease and frontotemporal dementia?**
A. *JPH*
B. *PRNP*
C. *SLC52A3* (also known as *C20ORF54*)
D. *VCP*

**29. Which of the following is the *least* likely presentation of metabolic myopathy?**
A. Muscle cramps during brief exercise
B. Muscle cramps during prolonged exercise
C. Myoglobinuria when the patient is febrile
D. Progressive lower extremity numbness

**30. A 1-month-old presents with poor feeding. On examination, he is hypotonic and has macroglossia and hepatomegaly. He is found to be in congestive heart failure. What is the most likely diagnosis?**
A. Congenital myotonic dystrophy
B. Central core disease
C. Myotubular myopathy
D. Pompe disease (acid maltase deficiency)

**31. A 30-year-old man presents with progressive weakness of the hands and feet. He says he also has difficulty releasing objects. On examination, he has frontal balding, ptosis, bilateral cataracts, masseter wasting, facial weakness, and weak distal extremities. A mutation in which of the following genes is most likely?**
A. *DMPK*
B. *GBE1*
C. *MT-TK*
D. *TIM*

**32. Which of the following statements about differences between myotonic dystrophy type 1 (DM1) and myotonic dystrophy type 2 (DM2) is most accurate?**
A. DM2 tends to cause proximal muscle weakness rather than distal.
B. DM2 tends to affect type 2 muscle fibers instead of type 1.
C. Systemic manifestations are typically less severe in DM2.
D. All of the above are true.

**33. A child presents with muscle stiffness. On examination, his leg muscles appear hypertrophied. His stiffness improves with activity. On electromyography (EMG), a "dive bomber" sound is heard. During the short exercise test, a postexercise decrement in the compound muscle action potential is seen, followed by a rapid return to baseline. Which of the following is the most likely etiology?**
A. A calcium channel mutation
B. A chloride channel mutation
C. A sodium channel mutation
D. A potassium channel mutation

**34. A 20-year-old man presents with abnormal eye movements. On examination, he has bilateral ptosis with no fatigability and limited eye movement when tracking. He also has hearing loss and pigmentary retinopathy. He has mild weakness in the proximal upper extremities. Which of the following is most likely to occur in this condition?**
A. Glaucoma
B. Pulmonary fibrosis
C. Ragged red fibers
D. Renal artery stenosis

**35. A patient with Sjögren syndrome presents with fever, fatigue, and weakness. On examination, the patient has periorbital edema, a facial rash, and a rash on her hands (extensor surface). She has proximal muscle weakness. Anti-Jo-1 antibodies are present in the serum. Which of the following findings is expected on muscle biopsy?**
A. Infiltration of the muscle by CD8$^+$ T lymphocytes
B. Perifascicular atrophy
C. Rimmed vacuoles
D. Intranuclear inclusions

**36. Humoral attacks on blood vessels, complement deposition, and capillary dropout are most likely to occur in which inflammatory myopathy?**
A. Antisynthetase syndrome
B. Inclusion body myositis (IBM)
C. Dermatomyositis
D. Polymyositis

**37. A 60-year-old woman presents with difficulties with stairs. She also complains that she is not able to knit like she used to. On examination, she has quadriceps weakness and asymmetric atrophy of her wrist and finger flexors. What is the most likely diagnosis?**
A. Amyloidosis
B. Inclusion body myositis
C. Immune-mediated necrotizing myopathy
D. Polymyositis

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**38. Which of the following conditions is *least* likely to respond to corticosteroids?**

A. Dermatomyositis
B. Inclusion body myositis
C. Polymyositis
D. Immune-mediated necrotizing myopathy

**39. Fill in the blank: Statin-induced myositis has been associated with reduced levels of ____________________?**

A. Coenzyme Q10
B. Pyridoxine
C. Vitamin $B_{12}$
D. Vitamin E

**40. Which type of fibers are slow twitch and fatigue resistant and use oxidative metabolism?**

A. Type 1
B. Type 2

**41. What do "onion bulbs" represent?**

A. An inflammatory reaction
B. A reaction to blunt trauma
C. Demyelination and remyelination
D. Ischemic injury to the nerve

**42. Which of the following is most suggestive of a myopathic process on muscle biopsy?**

A. Atrophic angular fibers
B. Group atrophy
C. Fibrosis
D. Target fibers

**43. Which pathologic finding is *least* likely to be found in a myopathy?**

A. Central nuclei
B. Fiber-type grouping
C. Split fibers
D. Small and large round fibers

**44. Internal nuclei are most prominent in which of the following?**

A. Myotonic dystrophy
B. Central core disease
C. Nemaline rod myopathy

**45. Which stain is most helpful for identifying glycogen storage diseases?**

A. Gomori trichrome stain
B. Congo red stain
C. Crystal violet stain
D. Periodic acid–Schiff (PAS) stain

**46. A 20-year-old woman presents with double vision. On examination, she has ptosis that worsens with prolonged upgaze. MG is suspected. Which of the following is the most sensitive test for MG?**

A. Cooling test
B. Repetitive nerve stimulation (RNS)
C. Single-fiber EMG of the frontalis muscle
D. Inching

**47. The majority of patients with MG have which type of antibody?**

A. Acetylcholine receptor binding antibodies
B. Acetylcholine receptor modulating antibodies
C. Acetylcholine receptor blocking antibodies

**48. Which of the following statements regarding myasthenic crisis is *false*?**

A. It is more common early in the disease course than later.
B. Initiation of steroids can trigger a myasthenic crisis.
C. Patients with acetylcholine receptor binding antibodies are at greater risk for myasthenic crisis than patients with muscle-specific tyrosine kinase (MuSK) antibodies.
D. Anticholinesterase medications should be withheld while the patient is intubated.

**49. A 50-year-old man presents with proximal leg weakness and dry mouth. Rapid repetitive nerve stimulation produces a significant increment. The patient most likely has which of the following cancers?**

A. Prostate cancer
B. Small cell lung cancer
C. Pancreatic cancer
D. Multiple myeloma

**50. Which of the following findings is more characteristic of MG than of Lambert–Eaton syndrome (LES)?**

A. Strength improves with repetition
B. Ocular weakness
C. Dry mouth
D. Abnormal pupillary response

**51. For each of the following, state whether it is usually a feature of an axonal neuropathy or a demyelinating neuropathy.**

1) Reduced compound muscle action potentials
2) Significantly reduced conduction velocities

**52. A woman presents with numbness in her feet. On examination, she has decreased sensations of pinprick and vibration. The results of a comprehensive metabolic profile, thyroid function tests, $B_{12}$ level, and hemoglobin A1c are normal. Which of the following should be performed next?**

A. Glucose tolerance test
B. HIV testing
C. Nerve biopsy
D. Vitamin E level

**53. A 20-year-old woman presents with wrist drop. She also had an episode of foot drop 3 months ago. Her mother and her sister have had similar experiences. A mutation in which of the following genes is responsible?**

A. *GDAP1*
B. *GJ1B*
C. *MPZ*
D. *PMP22*

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**54. Which of the following is *not* an X-linked inherited neuropathy?**

A. Charcot–Marie–Tooth neuropathy X type 1 (*GJB1*-related Charcot–Marie–Tooth neuropathy)
B. Fabry disease
C. Kennedy disease
D. Friedreich ataxia

**55. A patient with leukemia develops foot drop after a single dose of vincristine. Nerve conduction studies (NCSs) show a demyelinating polyneuropathy. A mutation in which of the following genes is most likely responsible?**

A. *HINT1*
B. *MFN2*
C. *PMP22*
D. *RAB7A*

**56. Which of the following is *least* likely to be seen in patients with Friedreich ataxia?**

A. Abnormal sensory NCSs
B. GAA triplet repeat expansion
C. Significantly reduced compound muscle action potentials
D. Square-wave jerks

**57. A patient presents with difficulty walking, which has been worsening over the past few days. He states that his legs initially became weak, but now his arms seem weak as well. Sensation is intact. He has areflexia. The cerebrospinal fluid (CSF) protein level is high, but the CSF white blood cell count is normal. Which of the following diagnoses is most likely?**

A. Spinal cord compression
B. Cervical spondylosis
C. Transverse myelitis
D. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)

**58. Which of the following is often the first abnormal finding in NCSs in AIDP?**

A. Prolonged F-wave latencies
B. Conduction block
C. Temporal dispersion
D. Significantly decreased amplitude of the compound muscle action potential (CMAP)

**59. Which Guillain–Barré syndrome (GBS) variant is characterized by ophthalmoparesis, areflexia, and ataxia and tends to be associated with GQ1b antibodies?**

A. Acute motor axonal neuropathy (AMAN)
B. Acute motor–sensory axonal neuropathy (AMSAN)
C. Bickerstaff brainstem encephalitis
D. Miller–Fisher variant
E. Sensory GBS

**60. Which of the following causes a descending paralysis?**

A. Botulism
B. Diphtheria
C. Tick paralysis
D. Porphyria

**61. True or false?**

Sensory disturbances are more common in chronic inflammatory demyelinating neuropathy (CIDP) than in AIDP.

**62. Which of the following disorders is most likely to be symmetric?**

A. Subacute inflammatory demyelinating polyneuropathy (SIDP)
B. Multifocal motor neuropathy (MMN)
C. Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM)

**63. Which of the following conditions is most likely to respond to steroids?**

A. AIDP
B. AMAN
C. MMN
D. MADSAM

**64. Which of the following is most consistent with immunoglobulin M–monoclonal gammopathy of undetermined significance (IgM-MGUS)?**

A. Asymmetric distal polyneuropathy
B. Symmetric proximal polyneuropathy
C. Slowed conduction velocities consistent with demyelination
D. Decreased amplitudes of compound muscle action potentials

**65. Which of the following systemic diseases is most closely associated with the syndrome of polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes (POEMS)?**

A. Lymphoma
B. Osteosclerotic myeloma
C. Small cell lung cancer
D. Thymoma

**66. A 50-year-old man presents with hand weakness. On examination, he has atrophy and fasciculations in his left hand, brisk reflexes in all four extremities, a brisk jaw jerk, and a normal sensory examination. Which of the following is the most likely diagnosis?**

A. Amyotrophic lateral sclerosis (ALS)
B. Primary lateral sclerosis
C. Progressive muscular atrophy
D. Spinal muscular atrophy (SMA)

**67. Which of the following conditions is most likely to be present in a patient with early ALS?**

A. Autonomic disturbance
B. Incontinence
C. Ophthalmoplegia
D. Spasticity

**68. What is the mechanism of action of riluzole?**

A. It is a γ-aminobutyric acid antagonist.
B. It inhibits glutamate release.
C. It is a glycine agonist.
D. It is an *N*-methyl-ᴅ- aspartate antagonist.

**69. A 40-year-old man with a history of diabetes mellitus (DM) presents with difficulty swallowing. On examination, he has perioral and tongue fasciculations, proximal weakness, and gynecomastia. A mutation in which of the following genes is most likely responsible?**

A. Androgen receptor gene
B. Estrogen receptor gene
C. Insulin receptor gene
D. Testosterone receptor gene

**70. An infant presents with developmental delay. The patient is alert but has proximal muscle weakness, areflexia, a bell-shaped chest, a frog-leg posture, and polyminimyoclonus. The newborn screen was reported to be abnormal, but the results are not available. Serum creatinine levels are low. Which of the following should be performed first in order to find the diagnosis?**

A. EMG/NCS
B. Muscle biopsy
C. Test for homozygous deletions in exons 7 and 8 in *SMN1*
D. DNA methylation analysis

**71. Which of the following is most likely to cause a demyelinating neuropathy?**

A. Amiodarone
B. Chloroquine
C. Metronidazole
D. Vinka alkaloid

**72. A 21-year-old male presents with arm atrophy. His weakness is asymmetric and most significant in the C8–T1 myotomes. Magnetic resonance imaging (MRI) shows mild atrophy of the lower cervical cord, loss of posterior dural attachment, ventral displacement of the cord with flexion, and a prominent posterior epidural venous plexus. Which of the following is recommended for this condition?**

A. Carnitine supplementation
B. Cervical collar
C. Echocardiogram
D. Measure insulin-like growth factor 1.
E. Measure transactive response DNA-binding protein 43 (TDP-43).

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# NEUROMUSCULAR DISEASES

## ANSWERS

**1. C**

The dorsal scapular nerve and the long thoracic nerve are proximal to the formation of the brachial plexus. The dorsal scapular nerve (C4, C5) supplies the major and minor rhomboid muscles. The long thoracic nerve (C5, C6, C7) supplies the serratus anterior.

The suprascapular nerve and nerve to the subclavius arise from the upper trunk.

The lateral pectoral nerve is a branch of the lateral cord, which is derived from the anterior branches of the upper and middle trunks of the brachial plexus.

**2. B**

The long thoracic nerve, which innervates the serratus anterior, can be injured during mastectomy. This results in scapular winging. Pressure on the shoulder from heavy objects can also injure the long thoracic nerve. In addition, the long thoracic nerve is often affected in Parsonage–Turner syndrome.

Parsonage–Turner syndrome, which is also known as neuralgic amyotrophy, tends to occur after a viral infection, immunization, or surgery. The patient has sudden, severe shoulder pain that often begins at night. This is followed by weakness of the shoulder and proximal arm. The phrenic nerve or anterior interosseous nerve may also be affected. There is a hereditary form.

Serratus anterior weakness causes medial winging of the scapula. Lateral winging of the scapula can be caused by weakness of rhomboid or trapezius muscles. The rhomboid muscles are innervated by the dorsal scapular nerve. The trapezius muscle is innervated by the spinal accessory nerve, C3, and C4. The spinal accessory nerve can be injured during cervical lymph node biopsy or other surgery in the cervical region. Trapezius weakness causes shoulder drop as well as scapular winging.

Scapular winging can also occur in myopathies. Sarcoglycanopathies and recessive limb–girdle muscular dystrophy type 1, or LGMDR1 calpain3-related (formerly limb–girdle muscular dystrophy 2A), are associated with scapular winging.

**3. C**

Wrist drop can occur with central nervous system lesions and with lesions of the C7 root, posterior cord of the brachial plexus, radial nerve in the axilla, radial nerve at the spiral groove, or posterior interosseous nerve.

**4. A**

The branches of the posterior cord are the radial nerve, the axillary nerve, the thoracodorsal nerve, and the subscapular nerve. To differentiate a posterior cord plexopathy from a radial neuropathy, a muscle innervated by the axillary, thoracodorsal, or subscapular nerve should be tested.

Testing shoulder abduction may help differentiate posterior cord plexopathy from radial neuropathy. The deltoid, which is innervated by the axillary nerve, is one of the muscles responsible for shoulder abduction. Weakness of shoulder abduction would make a posterior cord plexopathy lesion more likely than a radial neuropathy. Loss of sensation in the upper arm is also seen with axillary nerve injury.

The radial nerve is responsible for elbow and wrist extension. One of its branches, the posterior interosseous nerve, is responsible for finger extension.

**5. C**

The supraspinatus muscle, which is innervated by the suprascapular nerve (C5, C6), abducts the shoulder through the first 15 degrees. The deltoid muscle, which is innervated by the axillary nerve (C5, C6), abducts the arm from 15 to 90 degrees. The trapezius and serratus anterior muscles are involved in abduction of the arm from 90 to 180 degrees.

**6. B**

This patient has injured the radial nerve in the spiral groove, which is the most common site of radial nerve injury. The radial nerve can be injured at the spiral groove as a result of fracture of the humerus. “Saturday night palsy” is caused by injury of the radial nerve in the spiral groove.

The radial nerve can be injured at multiple locations. Knowledge of radial nerve anatomy allows prediction of the site of injury (see Box 16.1).

When the radial nerve is injured in the spiral groove, the patient has finger drop, wrist drop, and sensory changes in the distribution of the superficial radial sensory nerve. Supination is mildly weak. Weakness of the brachioradialis causes weakened elbow flexion. Elbow extension is spared because the triceps is not affected by a radial neuropathy at the spiral groove. The triceps is affected by radial nerve injury in the axilla, such as from crutches. Patients with radial neuropathy in the axilla also have decreased sensation in the posterior arm and forearm.

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### *Box 16.1* RADIAL NERVE ANATOMY

- The radial nerve is a branch of the posterior cord of the brachial plexus.
- In the upper arm, the radial nerve gives off cutaneous branches and innervates the triceps and anconeus muscles.
- The radial nerve then travels through the spiral groove of the humerus.
- Distal to the spiral groove but above the elbow, the radial nerve innervates the brachioradialis and extensor carpi radialis longus.
- Distal to the elbow, the radial nerve divides into the superficial radial sensory nerve and the deep radial motor branch.
- The *superficial radial sensory nerve* is typically a pure cutaneous sensory nerve. It supplies the lateral dorsum of the hand and part of the thumb.
- The *deep radial motor branch* supplies the extensor carpi radialis brevis and the supinator before traveling under the arcade of Frohse through the supinator muscle.
- When it travels into the supinator, the nerve becomes the *posterior interosseous nerve*, which is a pure motor nerve. The posterior interosseous nerve supplies the extensors of the wrist, thumb, and fingers.

**7. A**

This patient has carpal tunnel syndrome, which is caused by median nerve compression. It is the most common entrapment neuropathy. It is a clinical diagnosis. In idiopathic cases, the dominant hand is usually affected more than the nondominant hand. Nocturnal hand paresthesias are a common symptom. Sensory changes occur before motor changes. Patients have decreased sensation in the first, second, third, and fourth digits, with sparing of the medial side of the fourth digit. Sensation over the thenar eminence should be normal because it is innervated by the palmar cutaneous sensory branch of the median nerve, which arises before the carpal tunnel. Weakness of thumb abduction and opposition occur late.

A cervical radiculopathy is in the differential diagnosis of carpal tunnel syndrome. Pain in the neck, paresthesias from the neck or shoulder down the arm, weak arm muscles, sensory disturbances in the arm or forearm, and reduced biceps or triceps reflexes raise concern for a radiculopathy.

**8. B**

Ulnar nerve lesions do not cause sensory symptoms proximal to the wrist. The ulnar nerve provides no sensation proximal to the wrist.

The ulnar nerve does not travel through the carpal tunnel. It travels through Guyon's canal at the wrist. A proximal canal lesion causes ulnar palmar sensory loss and weakness of all the ulnar-innervated intrinsic hand muscles.

In Guyon's canal, the ulnar nerve splits into the superficial and deep branches. The superficial branch exits the canal, supplies the palmaris brevis (a hypothenar muscle), and provides sensation to the fourth and fifth digits. Fibers from the deep branch exit Guyon's canal to supply the other hypothenar muscles: the abductor digiti minimi, the flexor digiti minimi, and the opponens digiti minimi. After exiting Guyon's canal via the pisohamate hiatus, the deep branch supplies the rest of the ulnar-innervated muscles in the hand (the third and fourth lumbricals, the palmar interossei, the adductor pollicis, and the deep head of the flexor pollicus brevis). Therefore, a lesion at the pisohamate hiatus causes weakness of ulnar intrinsic hand muscles but spares the hypothenar muscles.

Ulnar neuropathy at the elbow can cause atrophy of hypothenar and thenar muscles, but thumb abduction is spared. Weakness of the flexor digitorum profundus can cause difficulty making a fist; the patient is unable to tuck in the fourth and fifth digits. The patient may demonstrate a benediction posture of the hands. Froment's sign and Wartenberg's sign may be seen. (Froment's sign is characterized by flexion of the thumb and index finger when pinching paper. Wartenberg's sign is caused by difficulty adducting the little finger: The little finger is abducted when the patient tries to hold the fingers together.)

**9. A**

The adductor magnus has innervation from the obturator nerve and the tibial division of the sciatic nerve.

The gluteus maximus is supplied by the inferior gluteal nerve.

The short head of the biceps femoris is the only muscle above the knee supplied by the peroneal division of the sciatic nerve.

The pectineus is innervated by the obturator and femoral nerves. It is an adductor of the thigh.

**10. A**

This patient has meralgia paresthetica, which is caused by compression of the lateral femoral cutaneous nerve. This nerve can be compressed under the inguinal ligament. Common risk factors include diabetes, obesity, pregnancy, constricting clothing, and trauma.

**11. C**

This patient has an S1 radiculopathy. S1 provides sensation to the sole and the lateral aspect of the foot. S1 also provides innervation to the hip extensors (gluteus maximus), knee flexors (hamstrings), plantar flexors (gastrocnemius and soleus muscles), toe flexors (flexor digitorum longus), and intrinsic foot muscles. The patient's ankle jerk reflex is reduced because the gastrocnemius muscle is affected.

An L4 radiculopathy would cause a decreased knee jerk. The quadriceps muscle is responsible for the knee jerk.

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**12. D**

The most common pattern of muscle weakness in myopathies is symmetric weakness in the proximal arms and legs.

**13. C**

If progression occurs in a congenital myopathy, it is slow, not rapid.

Causes of hypotonia and weakness in the newborn include congenital myopathies, congenital muscular dystrophies (CMDs), congenital myotonic dystrophy, congenital myasthenic syndromes, spinal muscular atrophy, acid maltase deficiency (Pompe disease), and Prader–Willi syndrome.

Congenital myopathies tend to be manifested at birth with hypotonia, weakness, and hyporeflexia. Facial, bulbar, extraocular, or respiratory weakness may be present. Ptosis occurs in many types of congenital myopathy. Orthopedic abnormalities may be present. Mental status and sensation are normal. The serum CK level is normal or slightly elevated; significant elevations are more consistent with muscular dystrophy. (In general, congenital myopathies tend to involve proteins in the contractile matrix or proteins involved in excitation–contraction coupling. In contrast, muscular dystrophies often affect proteins that help stabilize the cytoskeletal matrix to the sarcolemmal membrane and the extracellular matrix. Destabilization of the sacrolemmal membrane in muscular dystrophies leads to leakage of creatinine kinase, causing an elevated level. In congenital myopathy, the sarcolemmal membrane is more likely to be maintained.[1])

In an older child, congenital myopathy may manifest with scoliosis, a rigid spine, cardiomyopathy, pes cavus or foot drop, malignant hyperthermia, or respiratory weakness. Cardiomyopathy is not universal. Patients with mutations in *MYH7* or *TTN* are the most likely to have cardiac involvement. (*MYH7* encodes slow skeletal β-cardiac myosin, and *TTN* encodes titin.)[2]

Nemaline rod, core, and centronuclear myopathies are among the most common congenital myopathies.[1] Historically, muscle biopsy was used to help diagnose and classify congenital myopathies (see Table 16.1).

*Table 16.1* **CLASSIFICATION OF CONGENITAL MYOPATHIES BY MUSCLE BIOPSY FINDINGS**

| MUSCLE BIOPSY FINDING | DISEASES |
|---|---|
| **Rods** | **Nemaline rod myopathy** |
| **Cores** | **Central core disease, multi-minicore disease** |
| **Central nuclei** | **Centronuclear/myotubular myopathy** |
| **Hypotrophy of type 1 fibers** | **Congenital fiber-type disproportion** |

Currently, genetics, muscle MRI, and muscle ultrasound also aid in diagnosis of congenital myopathy. Genetic testing is complicated by the fact that multiple genes can cause a similar phenotype (genetic heterogeneity) and a genetic mutation can cause variable phenotypes (phenotypic pleiotropy). For instance, multiple genes have been found to cause nemaline myopathy. Also, mutations in *ACTA1*, which encodes α-skeletal actin (also known as skeletal muscle α-actin), can cause multiple types of congenital myopathy.[3]

**14. B**

This patient has central core disease, which is often caused by mutations in the *RYR1* gene on chromosome 19q. Mutations in *RYR1* can cause both congenital myopathy and a phenotype resembling congenital muscular dystrophies.[3,4] In addition to central core disease, mutations in this gene can cause multi-minicore disease, centronuclear myopathies, and cone–rod disease. *RYR1* mutations are also associated with hip dislocation, club feet, scoliosis, and rigid spine.

The *RYR1* gene encodes the ryanodine receptor that is found in muscle. This is a calcium channel receptor. Mutations in the *RYR1* gene are associated with malignant hyperthermia.

Inhalational agents, such as halothane, and the muscle relaxant succinylcholine can cause malignant hyperthermia in susceptible individuals. In the operating room, a rising end-tidal carbon dioxide level is an early sign of malignant hyperthermia. Other signs of malignant hyperthermia are hyperthermia, muscle rigidity, tachycardia, metabolic acidosis, hyperkalemia, and myoglobinuria due to rhabdomyolysis. Malignant hyperthermia is treated with cooling, fluids, and dantrolene. Dantrolene inhibits intracellular calcium release. It should not be given with calcium channel antagonists.

Cap myopathy and zebra body myopathy are types of nemaline rod myopathy.

**15. B**

This patient has nemaline myopathy. The age of onset and severity of nemaline myopathy are variable, and there is genetic heterogeneity, but patients with nemaline myopathy share the same histopathological finding.

Defects in multiple genes cause nemaline myopathy, most commonly mutations in *NEB*, which encodes nebulin. Severe cases of nemaline myopathy are often the result of mutations in *ACTA1*.[3]

**16. C**

The congenital muscular dystrophies (CMDs) tend to cause delayed motor milestones and hypotonia and muscle weakness prior to ambulation. The CMDs are associated with pathological findings such as variation in muscle fiber size, muscle fiber degeneration and regeneration, and fibrosis. There is variable involvement of cardiac muscle, respiratory muscle, the central nervous system, and the eyes.[5]

Common CMDs include collagenopathies (e.g.,collagen VI–related disorders), dystroglycanopathies (e.g., Fukuyama CMD), selenoprotein N–related myopathy, and merosinopathies.

Merosin-deficient CMD is the most common CMD in the European population.[1] It is also referred to as MDC1A. Merosin-deficient CMD/MDC1A is caused by mutations in *LAMA2*, which encodes laminin-$\alpha_2$.[4,6] It manifests with weakness, hypotonia, respiratory insufficiency, and feeding difficulties. Contractures may be present at birth. Central nervous system abnormalities such as seizures and dysmyelination can occur. The MRI of these patients can resemble a leukodystrophy, but upper motor neuron signs are typically lacking.[1]

Merosin (also known as laminin-211) is an extracellular protein, specifically a cell adhesion molecule, in the skeletal muscle basement membrane. It mediates attachment of components of the extracellular matrix to the sarcolemmal membrane through an interaction with α-dystroglycan.[1] Merosin is also found in the brain.

CMD may be due to defects in structural proteins of the basal membrane or extracellular matrix such as LAMA2-related disorders and collagen V1/COL6–related disorders; defects in dystroglycan, α-dystroglycan, or glycosyltransferase enzymes such as Walker–Warburg syndrome, muscle–eye–brain disease, and Fukuyama CMD; defects in endoplasmic reticulum proteins such as selenoprotein N–related myopathy/CMD with spinal rigidity; defects in nuclear envelope proteins; defects in mitochondrial membrane proteins; and defects in external sarcolemmal proteins.[5,7] The largest group of CMDs is the group of diseases associated with defects in dystroglycan, α-dystroglycan, and glycosyltransferase enzymes.[1] (See Box 16.2.)

### *Box 16.2* CAUSES OF CONGENITAL MUSCULAR DYSTROPHY5,7

- Defects in basal membrane or extracellular matrix proteins
- Defects in dystroglycan, α-dystroglycan, and glycosyltransferase enzymes
- Defects in endoplasmic reticulum proteins
- Defects in nuclear envelope proteins
- Defects in mitochondrial membrane protein
- Defects in external sarcolemmal protein

Defects in nuclear envelope proteins can also cause Emery–Dreifuss muscular dystrophy (EDMD). Defects in sarcolemmal and sarcomeric proteins can also cause LGMDs.[7]

### 17. True

Botulinum toxin can cause prolonged weakness in patients with CMD; therefore, it may need to be avoided unless the patient's contractures cause significantly more impairment than prolonged weakness would.[6]

### 18. D

There is variable cardiac involvement in CMDs. Merosin-deficient CMD, Fukuyama CMD, and selenoprotein N–related myopathy/SEPN1-related myopathy/CMD with spinal rigidity (formerly rigid spine muscular dystrophy 1) can all have cardiac involvement.

In a patient with muscle disease, an elevated level of CK-MB does not necessarily indicate cardiac involvement.

### 19. D

Ocular involvement and seizures are most common in the dystroglycanopathies but can also occur in patients with merosin-deficient CMD. Lissencephaly type II/pachygyria can be seen in Fukuyama CMD, muscle–eye–brain disease, and Walker–Warburg syndrome, which are dystroglycanopathies. An occipital encephalocele can occur in patients with Walker–Warburg syndrome, which is the most severe of the dystroglycanopathies. Cerebellar cysts are seen in some dystroglycanopathies.[4,6]

### 20. D

This is selenoprotein N–related myopathy/SEPN1-related myopathy/CMD with spinal rigidity, which is caused by mutations in *SELENON* (also known as *SEPN1*). This condition often manifests with poor head control.

Early respiratory compromise can occur in patients with selenoprotein N–related myopathy, collagen VI–related dystrophies, and LMNA-related dystrophy.[1] Both selenoprotein N–related myopathy and collagen VI–related dystrophies can cause unexpected respiratory failure and cor pulmonale.

Collagen VI–related dystrophies are also associated with congenital contractures and excessive laxity. These dystrophies tend to cause proximal contractures, distal joint hyperlaxity, weakness, and skin changes.[1] Examples of collagen VI–related dystrophies are Ullrich CMD and Bethlem myopathy. Both can be associated with hyperkeratosis and keloid formation.

Head drop and spinal rigidity also occur in LMNA-related dystrophy, but the CPK level is higher in these patients than in patients with selenoprotein N–related myopathy/SEPN1-related myopathy. LMNA-related dystrophy is caused by mutations in lamin A/C, which is encoded by *LMNA*. Lamin A/C mutations can also cause EDMD.[4]

### 21. C

This patient has Duchenne muscular dystrophy (DMD). This can present with gross motor delays, such as delayed walking, or abnormal gait, including persistent toewalking. Corticosteroids prolong ambulation. Deflazacort causes less weight gain than prednisone but has a higher risk for cataracts.

DMD is one of the dystrophinopathies. It is usually caused by out-of-frame mutations in *DMD*, which encodes for the protein dystrophin. In-frame mutations cause Becker muscular dystrophy (BMD). Both DMD and BMD are X-linked recessive.

Patients with DMD gradually lose motor milestones and become wheelchair bound. They develop joint contractures and scoliosis. DMD is associated with decreased pulmonary function, cardiac arrhythmias and dilated cardiomyopathy, and cognitive impairment. Female carriers of DMD can also develop dilated cardiomyopathy.

BMD is less severe, and intellect is typically normal.

Dystrophin restoration approaches for DMD include antisense oligonucleotide inducers of exon skipping, stop codon readthrough, adeno-associated virus-mediated gene therapy, stem cell therapies, and upregulation of dystrophin surrogate proteins.[8]Current exon skipping therapies (e.g., eteplirsen, golodirsen, casimersen, and viltolarsen) do not benefit all Duchenne patients; these can only be used in patients with certain mutations. Adeno-associated virus vectors, such as delandistrogene moxeparvovec-roki, do not have the capacity to accommodate full-length dystrophin cDNA, and immunity against adeno-associated viruses may interfere with treatments using this delivery system.[8]

**22. C**

This patient has facioscapulohumeral dystrophy (FSHD). The first sign is usually facial weakness, but arm weakness with difficulty performing overhead activities is more likely to bring the patient to medical attention. The pectoral muscles are particularly weak, resulting in reversal of the anterior axillary folds. A "triple hump" sign can be seen because of preserved deltoid strength and scapular winging. (The humps are the deltoid, the shoulder bones, and the winged scapula.) Surgery may be required to fix the scapula in place. Weak abdominal muscles can cause abdominal protuberance. The rectus abdominius and semimembranosus muscles are severely affected in FSHD.[9]

Cardiomyopathy, respiratory insufficiency, and bulbar weakness are not common in FSHD, although some patients have cardiac arrhythmia. Life expectancy is typically normal. Hearing loss and retinal vascular abnormalities are common in FSHD. Patients with large deletions on 4q are at increased risk for these.[9] Patients with FSHD can have Coat syndrome, which refers to an exudative retinopathy.

**23. D**

This patient has oculopharyngeal muscular dystrophy (OPMD), which causes ptosis and dysphagia. Patients often have ophthalmoparesis as well, but diplopia is rare. OPMD usually manifests in the fifth or sixth decade of life with ptosis. It is associated with expansion of the GCN trinucleotide repeat in the gene *PABPN1*, which encodes for polyadenylation-binding protein nuclear 1. OPMD is autosomal dominant. Anticipation does *not* occur in OPMD.

Facioscapulohumeral dystrophy and myotonic dystrophy usually do not cause ophthalmoplegia.

Mitochondrial myopathy tends to cause ptosis and ophthalmoplegia without pharyngeal involvement.

The combination of ptosis and ophthalmoparesis can occur in other myopathies and in neuromuscular junction (NMJ) disorders such as MG. Weakness may fluctuate in patients with NMJ disorders. Certain congenital myopathies, such as nemaline myopathy and central core myopathy, cause ptosis without ophthalmoparesis.

**24. A**

Facial weakness is most likely to be asymmetric in facioscapulohumeral dystrophy (FSHD). In FSHD, weakness begins in the face and spreads in a rostrocaudal pattern. Limb muscle involvement may also be asymmetric. There may be highly variable clinical phenotypes among different family members with FSHD.

Most cases of FSHD are classified as FSHD1, which has multiple specific genetic features. Patients with FSHD1 have a contraction mutation of *D4Z4* on chromosome 4 that results in fewer repeats than normal. In addition, a permissive simple sequence length polymorphism and the 4qA variant at the terminus must be present for the disease to manifest clinically. The combination of these genetic features leads to hypomethylation of the D4Z4 region. This region contains the *DUX4* gene, which encodes double homeobox protein 4 (DUX4). Type 2 FSHD is caused by mutations in the *SMCHD1* gene. Mutations in the *SMCHD1* gene also affect DUX4 expression.[10]Both FSHD1 and FSHD2 are autosomal dominant.

In myotonic dystrophy, facial weakness causes ptosis and a "hatchet-face" or "fish-mouth" look. The mastication muscles are particularly affected.

MG can cause asymmetric weakness of eye movement and asymmetric ptosis.

**25. A**

This patient has Emery-Dreifuss muscular dystrophy (EDMD). Early contractures of the elbow flexors and ankle plantar flexors are characteristic findings. Contractures of the spine also occur early. Patients have a humeroperoneal pattern of weakness and cardiac disease. Patients with EDMD are at risk for sudden death. They may require a pacemaker with an internal cardiac defibrillator.

Most patients with EDMD have mutations in the gene *LMNA*, which encodes lamin A/C. This mutation is autosomal dominant. Other patients with EDMD have mutations in *EMD*, which encodes emerin. This is X-linked recessive. There are other, less common genetic mutations that can cause EDMD. Female carriers of X-linked EDMD are at risk for cardiac disease.

*SMN1* and *SMN2* both encode for survival motor neuron protein, which is discussed below.

Mutations in the gene *ZNF9* (also known as *CNBP*) cause myotonic dystrophy type 2 (DM2).

**26. C**

Typically, but not always, LGMDs affect the proximal muscles in the upper and lower extremities and have autosomal inheritance. Historically, autosomal dominant LGMDs were classified as type 1 and autosomal recessive LGMDs were classified as type 2. More recently, dominant forms are referred to as LGMDD and recessive forms are referred to as LGMDR. The autosomal recessive LGMDs are more common than those inherited in an autosomal dominant manner, have a younger age of onset, and are associated with a more rapid loss of strength and higher CK levels. (See Table 16.2.)

*Table 16.2* COMPARISON OF AUTOSOMAL DOMINANT AND AUTOSOMAL RECESSIVE LIMB–GIRDLE MUSCULAR DYSTROPHIES[11]

| AUTOSOMAL DOMINANT LIMB–GIRDLE MUSCULAR DYSTROPHIES | AUTOSOMAL RECESSIVE LIMB–GIRDLE MUSCULAR DYSTROPHIES |
|---|---|
| Less common | More common |
| Older onset | Younger onset |
| Chronically progressive | More rapid loss of strength |
| Normal or minimally elevated creatine kinase levels | Higher creatine kinase levels |

Patients with autosomal dominant LGMD may have a normal or minimally elevated CK. An exception is rippling muscle disease (LGMD1C), which causes a significantly elevated CK. Percussion with a reflex hammer elicits rippling muscles in these patients. Hypertrophic cardiomyopathy and cardiac arrhythmias can also occur in rippling muscle disease/LGMD1C.

LGMDD1 (formerly LGMD1D) is due to mutations in *DNAJB6*, which encodes a protein that has a chaperone function.[11]

One form of myofibrillar myopathy is caused by mutations in *MYOT*, which encodes myotilin; this was formerly LGMD1A. Dysarthria is a characteristic finding. Some patients have cardiomyopathy.

Patients with mutations in *DES*, which encodes desmin, can also have a form of myofibrillar myopathy; this was formerly called LGMD1E. These patients can have cardiomyopathy.[12,13]

Mutations in *LMNA*, which encodes lamin A/C, are one cause of EDMD. Patients with mutations in *LMNA* were formerly called LGMD1B. Limb contractures can be seen. These patients can also have significant cardiac disease; life-threatening arrhythmias and cardiomyopathy can occur.

**27. A**

Autosomal recessive LGMDs tend to be due to abnormal muscle structural, maintenance, or repair proteins.[11] Recessive LGMD type 1, or LGMDR1 calpain3-related (formerly LGMD2A), is the most common LGMD in most areas of the world and is due to an enzyme defect.[11,14]

Recessive LDMD type 1, or LGMDR1 calpain3-related (formerly LGMD2A), is associated with mutations in *CAPN3*,which encodes calpain-3, a proteolytic enzyme. Therefore, this LGMD is due to an enzyme defect rather than a defect in a structural protein.[14] (Mutations in *CAPN3* can also cause a dominant form of LGMD.) Most patients with LGMDR1 develop symptoms before adulthood. The proximal lower extremities are weaker than the upper extremities, but scapular winging is present. This condition is usually not associated with cardiac disease.

LGMDR2 dysferlin-related (formerly LGMD2B) is also a common type of LGMD. It is associated with gastrocnemius weakness as well as progressive shoulder and hip girdle weakness and may present with inability to stand/walk on the toes.[11] LGMDR2 dysferlin-related is associated with very high CK levels. It is caused by mutations in *DYSF*. Mutations in *DYSF* also cause Miyoshi myopathy. Miyoshi myopathy is characterized by distal weakness primarily affecting the calf muscles.

LGMDR9 FKRP-related (formerly LGMD2I) is caused by mutations in *FKRP,* which encodes fukutin-related protein (FKRP). FKRP is involved in the enzyme pathway for glycosylating $\alpha$-dystroglycan.[11] Therefore, LGMDR9 FKRP-related/LGMD2I may be considered one of the dystroglycanopathies. It is associated with scapular winging, calf hypertrophy, and early cardiorespiratory involvement. These patients often have exercise-induced muscle pain and may have myoglobinuria.[11]

Sarcoglycanopathies, which are recessive LGMD types 3–6, resemble dystrophinopathies. (Specifically, sarcoglycanopathies include LGMD2D/R3, LGMD2E/R4, LGMD2C/R5, and LGMD2F/R6). However, DMD and BMD are more common than LGMD. In sarcoglycanopathies, symptoms begin in childhood, and progressive proximal weakness occurs. Calf hypertrophy and lumbar hyperlordosis are seen. Normal cognitive function and scapular winging are more likely to occur in sarcoglycanopathies than in DMD and BMD.[14] Respiratory failure occurs late in the disease course of sarcoglycanopathies. Cardiac function is most likely to be affected in LGMD2E/R4.[11]

**28. D**

Mutations in the gene *VCP* cause inclusion body myopathy with Paget disease and frontotemporal dementia (IBMPFD1), which is also called multisystem proteinopathy 1. This disorder can also be associated with motor neuron disease. The gene *VCP* encodes valosin-containing protein, which is a type of adenosine triphosphatase.

Mutations in *SLC52A3* (previously called *C20ORF54*) are responsible for some cases of Fazio–Londe syndrome, which is also known as progressive bulbar palsy of childhood. *SLC52A3* encodes a riboflavin transporter, and there have been attempts to treat Fazio–Londe syndrome with riboflavin.

Mutations in *PRNP* and *JPH* cause Huntington disease–like 1 and Huntington disease like–2, respectively.

**29. D**

Metabolic myopathy can manifest with progressive weakness or exercise intolerance, such as cramps and myalgia. Myoglobinuria may occur with exercise or when the patient is febrile.

Metabolic causes of exercise intolerance include fatty acid oxidation disorders, defects of glycogenolysis, mitochondrial disorders, and myoadenylate deaminase deficiency. Brief exercise uses glycogen. Therefore, symptoms manifesting during a short amount of exercise suggest a glycogen storage disorder. Prolonged exercise requires free fatty acids. Symptoms that develop with prolonged exercise suggest a lipid storage disease.

Carnitine palmitoyl transferase II deficiency is the most common cause of recurrent myoglobinuria in adults. Triggers include fever, exercise, fasting, and valproic acid. The CK level is usually normal or mildly elevated between episodes.

Glycogen storage disease type V, or McArdle disease, also causes episodes of myoglobinuria. CK is elevated during and between episodes. Patients with McArdle disease may experience a second wind with exercise. Warming up before exercise and consuming a carbohydrate-rich diet may help with exercise tolerance. McArdle disease is caused by mutations in the gene that encodes myophosphorylase (*PYGM*).

Patients with glycogen storage disease type VII, or Tarui disease, have some similarities to those with McArdle disease. For example, patients with Tarui disease have exercise intolerance; however, patients with Tarui disease worsen if given glucose before exercise. Tarui disease is caused by deficiency of phosphofructokinase.[15]

**30. D**

This patient has Pompe disease, which is glycogen storage disease type II (GSD II). This is a lyosomal storage disease caused by acid maltase deficiency. The gene responsible for GSD II is *GAA*. GSD II can manifest in the newborn period with macroglossia, hypotonia, weakness, congestive heart failure, and hepatomegaly. It can manifest later in life with progressive proximal weakness. It can resemble a limb-girdle muscular dystrophy or polymyositis. GSD II/acid maltase deficiency can also manifest with respiratory failure. Myotonic discharges may be seen in the paraspinal muscles.

Enzyme replacement is available for late-onset Pompe disease; avalglucosidase alfa-ngpt has been approved for patients aged 1 year or older. Fluid overload is a risk.[16]

**31. A**

This patient has myotonic dystrophy type 1 (DM1), which is caused by an expanded CTG repeat in the *DMPK* (dystrophia myotonica protein kinase) gene on chromosome 19. Patients with adult-onset DM1 have grip myotonia, distal weakness, and a distinctive facial appearance. Specifically, patients with DM1 have frontal balding, ptosis, and wasting of the temporalis and masseter muscles. "Christmas tree" cataracts are characteristic of DM1. Myotonia, which causes a crescendo–decrescendo pattern (described as a "dive bomber" sound) on EMG, has been treated with mexiletine. Respiratory muscle weakness leads to pneumonia. Obstructive sleep apnea and sleep hypoventilation can occur. Modafinil has been used for hypersomnia. Arrhythmias may result in sudden death. Endocrine dysfunction is common (e.g., DM, hypogonadism, and hyperlipidemia). Patients may have complications from anesthesia. Cholelithiasis, constipation, and dysphagia can occur in DM1. Patients have been described as apathetic or may have an avoidant personality. Mild cognitive impairment may be present. Subcortical white matter changes can be seen on MRI.

DM1 is autosomal dominant. Anticipation occurs.

Congenital myotonic dystrophy is more severe than adult-onset DM1 and is usually inherited from the mother. Patients are hypotonic at birth and may have arthrogryposis. The mouth is often tent-shaped. Facial weakness causes poor suck. Reflexes are decreased or absent. Myotonia is *not* present in infancy; genetic testing confirms the diagnosis. Respiratory distress is common. Patients with congenital myotonic dystrophy have delayed milestones and cognitive impairment.

Mutations in *GBE1* cause glycogen storage disease type IV (GSD IV), which results in glycogen branching enzyme deficiency. This is also known as Anderson disease. Some patients with this condition have adult polyglucosan body disease, which is associated with dementia, upper and lower motor symptoms, and cerebellar ataxia.

Mutations in the gene *MT-TK* are associated with myoclonic epilepsy with ragged red fibers.

Mutations in *TIM* cause triosephosphate isomerase deficiency, which leads to hemolytic anemia and neurologic deterioration in early childhood.

**32. D**

DM1 is associated with the triad of distal muscle weakness, myotonia, and early cataracts.[17] Whereas DM1 tends to cause distal muscle weakness, DM2 causes proximal muscle weakness. (DM2 has been called proximal myotonic myopathy.) Patients with DM2 are less likely to have facial weakness than patients with DM1. Calf hypertrophy can be seen in DM2. DM2 causes muscle pain, stiffness, and weakness. Pain can be prominent.[17] Systemic manifestations are less common in DM2 than in DM1, but patients with DM2 can have arrhythmia, endocrine dysfunction, cataracts, and white matter changes. Both DM1 and DM2 are associated with an increased risk for cancer. Due to the complications of DM1 and DM2, patients with these conditions may benefit from the following testing: electrocardiogram, screen for sleep apnea (especially DM1), screen for dysphagia, glucose breath test to assess for bacterial overgrowth syndrome, slit-lamp examinations, thyroid testing, and age-appropriate cancer screening.[17]

In both DM1 and DM2, muscle biopsy shows increased internal nuclei, and pyknotic nuclear clumps can be seen. In DM1, type 1 fibers tend to be more affected. In DM2, type 2 fibers tend to be more affected. (See Table 16.3.)

DM2 is autosomal dominant, like DM1; however, DM2 does *not* demonstrate anticipation, which occurs in DM1. DM2 is caused by a quadruple nucleotide repeat (CCTG) in the *ZNF9* gene, which has also been called *CNBP*. In both DM1 and DM2, the repeat expansion is associated with sequestration of RNA-binding proteins.[17]

*Table 16.3* COMPARISON OF MYOTONIC DYSTROPHY TYPE 1 AND MYOTONIC DYSTROPHY TYPE 2

| MYOTONIC DYSTROPHY TYPE 1 | MYOTONIC DYSTROPHY TYPE 2 |
|---|---|
| CTG repeats | CCTG repeats |
| Anticipation occurs | No anticipation |
| Distal weakness | Proximal weakness |
| Type 1 muscle fibers more affected | Type 2 muscle fibers more affected |
| More systemic findings | Less systemic findings |
| Fatigue | Pain |

**33. B**

This is myotonia congenita, which is caused by a chloride channel mutation. The mutation is in the gene *CLCN1* on chromosome 7q35. Patients with myotonia congenita have muscle hypertrophy, especially in the legs, and myotonia. Clinically, myotonia improves with exercise, as in patients with myotonic dystrophy.

Myotonia worsens with exercise in patients with *para*-myotonia congenita, which is caused by a sodium channel mutation. Mutations in the gene *SCN4A* on chromosome 17q23 cause paramyotonia congenita, hyperkalemic periodic paralysis, hypokalemic periodic paralysis, and potassium-aggravated myotonias (myotonia fluctuans, myotonia permanens, and acetazolamide-sensitive myotonia). Dichlorphenamide is a carbonic anhydrase inhibitor used for treatment of primary hyperkalemic and primary hypokalemic periodic paralysis.

Andersen–Tawil syndrome and thyrotoxic periodic paralysis are caused by mutations in the potassium channel. Anderson–Tawil syndrome is characterized by distinctive facial features, ventricular arrhythmias, and episodic weakness. Flaccid weakness can occur in patients with Anderson–Tawil syndrome with high, low, or normal potassium levels. Hypokalemia can cause weakness in patients with thyrotoxic periodic paralysis.

**34. C**

This patient has Kearns–Sayre syndrome, which is caused by a deletion in mitochondrial DNA. Progressive external ophthalmoplegia and pigmentary retinopathy are characteristic.

Patients with Kearns–Sayre syndrome can have heart block and may require pacemakers. Patients also tend to have sensorineural deafness, a proximal myopathy, cerebellar ataxia, high CSF protein, and short stature. Endocrinopathies may be present. Patients may benefit from treatment with coenzyme Q10 and L-carnitine. Some patients have low CSF folic acid and have been given folinic acid.

Pearson syndrome is also caused by a mitochondrial DNA deletion and is associated with progressive external ophthalmoplegia. However, patients with Pearson syndrome also tend to have sideroblastic anemia and pancreatic dysfunction.

**35. B**

This patient has dermatomyositis, which is an inflammatory myopathy. Dermatomyositis occurs in both children and adults. It is more common in women than in men. Typical features are a heliotrope rash on the eyelids, Gottron papules on the knuckles, a sun-sensitive rash on the face and upper body, and subcutaneous calcifications over pressure points such as the elbows. Patients have symmetric proximal weakness in the upper and lower extremities. On muscle biopsy, perifascicular atrophy is seen. Gastrointestinal hemorrhage can occur from vasculopathy in dermatomyositis. Myocarditis and interstitial lung disease (ILD) are possible complications of dermatomyositis.

Anti-Jo-1 antibodies are often present in the serum of patients with inflammatory myopathy and ILD. However, ILD is usually most severe in patients with anti-MDA-5 dermatomyositis. (ILD is also severe in antisynthetase syndrome and overlap myositis with systemic sclerosis.)[18]

Patients with dermatomyositis and anti-Mi-2 antibody tend to have a more typical course and a good prognosis.[18]

Adults with dermatomyositis are at increased risk for cancer. Patients with juvenile dermatomyositis do not usually have this risk. Anti-TIF1 antibodies may be found in patients with dermatomyositis and cancer. Patients with this antibody can also have poikiloderma, alopecia, and severe photoerythema.[18]

Dermatomyositis is associated with autoimmune conditions such as systemic lupus erythematosus, Raynaud syndrome, and Sjögren syndrome. Anti-nuclear antibodies may be present in patients with dermatomyositis.

Sjögren syndrome is characterized by xerophthalmia (dry eyes) and xerostomia (dry mouth). Patients may have a small-fiber neuropathy. Salivary gland biopsy and the presence of anti-Ro (SSA) and anti-LA (SSB) antibodies help confirm the diagnosis of Sjögren syndrome.[19]

## 36. C

In addition to perifascicular atrophy, muscle biopsy in patients with dermatomyositis may demonstrate humoral attacks on blood vessels and complement deposition. Interferon-1 pathway dysfunction and vasculopathy occur in dermatomyositis, and capillary dropout occurs.[18]

Infiltration of the muscle by CD8$^+$ T lymphocytes is seen in polymyositis.

Rimmed vacuoles, intranuclear inclusions, and intracytoplasmic inclusions are found in IBM. Rimmed vacuoles can also occur in patients with certain types of muscular dystrophies (see Table 16.4).

*Table 16.4* COMPARISON OF PATHOLOGIC FINDINGS IN INFLAMMATORY MYOPATHIES

| DISEASE | MUSCLE BIOPSY FINDINGS |
|---|---|
| **Dermatomyositis** | **Perifascicular atrophy** |
| **Inclusion body myositis** | **Red-rimmed vacuoles on Gomori trichrome stain, CD8$^+$ lymphocytes in the endomysium** |
| **Polymyositis** | **CD8$^+$ lymphocytes infiltrating the muscle** |

Antisynthetase syndrome is characterized by myositis, ILD, mechanic's hands, Raynaud syndrome, arthralgias, and antibodies, most commonly anti-Jo-1.[18]

## 37. B

This patient has IBM. IBM affects the finger flexors and quadriceps. This may present with difficulty climbing stairs or arising from a chair. In the hand, the flexor digitorum profundus muscle tends to be involved early.[20]

Wrist flexors and ankle dorsiflexion may also be affected. The weakness tends to be asymmetric, which is unusual in autoimmune myopathies. Patients are at risk for falls and may have dysphagia. Red-rimmed vacuoles are seen on Gomori trichrome stain. CD8$^+$ T cell lymphocytes infiltrate the endomysium. There is some evidence that CD8$^+$ T cells with the killer cell lectin-like receptor G1 (KLRG1) marker have a role in the pathogenesis of IBM.[20] Antibodies to cytosolic 5′-nucleotidase 1A (NT5C1A) may be present in patients with IBM (see Table 16.5). Patients with these antibodies may have bulbar symptoms and a worse prognosis. Genetic risk factors for IBM include HLA DRB1*03:01 and *FYCO1* missense variants.[21]

*Table 16.5* ANTIBODIES IN INFLAMMATORY MYOPATHIES

| DISEASE | ANTIBODIES |
|---|---|
| **Dermatomyositis** | **Anti-Mi-2, anti-nuclear matrix protein 2 (anti-NXP-2), anti-transcription intermediary factor 1γ (anti-TIF1γ), anti-MDA-5, anti-SAE18** |
| **Inclusion body myositis** | **Cytosolic 5′-nucleotidase 1A (NT5C1A)** |
| **Immune-mediated necrotizing myopathy** | **Signal recognition particle (SRP), 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase, or more rarely antimitochondrial** |
| **Antisynthetase syndrome** | **Anti-Jo-1 is the most common** |

Immune-mediated necrotizing myopathy can occur in autoimmune conditions or malignancies. In some patients, it follows statin use. These patients may have antibodies to 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase. However, some patients with these antibodies are statin naive.[18] Some patients with immune-mediated necrotizing myopathy have anti–signal recognition particle (SRP) antibody, which can be associated with dilated cardiomyopathy.[19]Other patients with immune-mediated necrotizing myopathy may be antibody-negative.

## 38. B

Corticosteroids are used to treat dermatomyositis, polymyositis, and immune-mediated necrotizing myopathy. IBM does not respond to corticosteroids.

Methotrexate has also been used for dermatomyositis, polymyositis, and immune-mediated necrotizing myopathy. It does carry a risk for pulmonary fibrosis, so some recommend avoiding it in patients with dermatomyositis who have ILD or anti-Jo-1 antibodies.[19]

## 39. A

Statin-induced myositis has been associated with reduced levels of coenzyme Q10.

Certain mutations in the gene *SLCO1B1* indicate predisposition to statin myopathy. *SLCO1B1* encodes an organic anion transporter in the liver that is involved in processing statins.[22]

Testing for autoantibodies to 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase helps differentiate statin-associated toxic necrotizing myopathy from immune-mediated necrotizing myopathy; these antibodies occur in the immune-mediated form. Using cyclosporine and certain other cholesterol-lowering agents can increase the risk for toxicity from statins. Renal failure also increases the risk.[22]

Inflammatory myositis can also occur with immune checkpoint inhibitors, which are used to treat cancer. This myositis can affect the ocular muscles, causing ptosis or diplopia. It can be associated with limb–girdle weakness, myocarditis, and lymphopenia.[18] (Immune checkpoint inhibitors can also cause MG.)

Other medications that cause myopathy include zidovudine (AZT) and steroids. AZT can cause a mitochondrial myopathy associated with ragged red fibers. Steroid myopathy can occur in patients who are receiving steroids for other myopathies, such as inflammatory myopathies. EMG and muscle biopsy help differentiate steroid myopathy from inflammatory myopathies. Insertional activity is normal in steroid myopathy and may be abnormal in inflammatory myopathies. Steroid myopathy tends to affect type 2 muscle fibers.

Colchicine, chloroquine, hydroxychloroquine, and amiodarone can cause neuromyopathy (myopathy and neuropathy).[22]

**40. A**

Type 1 fibers are slow twitch and fatigue resistant; they use oxidative metabolism.

Type 2 fibers are fast twitch and fatigue prone; they use glycolytic metabolism. Usually, there are twice as many type 2 fibers as type 1 fibers.

**41. C**

Onion bulbs indicate demyelination and remyelination. They are seen in Charcot–Marie–Tooth disease (e.g., CMT1A). They are also seen in CIDP.

Tomaculi (focal hypermyelination) are seen in hereditary neuropathy with liability to pressure palsies (HNPP).

**42. C**

Of the features listed, fibrosis is the most suggestive of a myopathic process. Atrophic angular fibers, group atrophy, and target fibers are more suggestive of a neurogenic process. Target fibers, which indicate active denervation and reinnervation, can be seen in ALS.

**43. B**

Fiber-type grouping occurs in neuropathy. Muscle fibers that are reinnervated by an anterior horn cell assume the properties of that cell.

Central nuclei, split fibers, and the combination of small and large round fibers are more consistent with myopathy.

**44. A**

Internal nuclei are most prominent in myotonic dystrophy.

**45. D**

Periodic acid–-Schiff (PAS) stain identifies glycogen storage diseases.

Crystal violet and Congo red stains identify amyloid.

Oil red O identifies lipid and is helpful in the diagnosis of lipid storage diseases.

**46. C**

Fatigable weakness is characteristic of neuromuscular junction disorders such as MG.

Single-fiber EMG is the most sensitive test for MG. It shows increased jitter and blocking in MG. However, this is not specific for MG.

Cooling improves weakness in MG because of improved neuromuscular transmission.

Repetitive nerve stimulation (RNS) is used to help diagnose MG. RNS causes a compound muscle action potential (CMAP) decrement in MG. However, RNS may be normal in ocular MG.

Inching is an NCS technique for detecting focal demyelination.

**47. A**

Patients with MG can have binding, modulating, or blocking antibodies to the acetylcholine receptor.

Most patients with MG have acetylcholine receptor binding antibodies. These antibodies can also be found in other diseases at lower levels, such as in patients with systemic lupus erythematosus and in relatives of patients with MG.

Acetylcholine receptor modulating antibodies are often seen in MG patients with thymoma. Also, striated muscle antibodies are associated with an increased risk for thymoma. Some patients with MG may benefit from thymectomy even if there is no thymoma.

Children with MG are less likely to be seropositive than adults with MG. The absence of antibodies does not rule out MG. Lack of decrease in antibody levels with immunosuppressive therapy suggests that the therapy is not effective.

Patients with MG who are negative for acetylcholine receptor antibodies may have muscle-specific tyrosine kinase (MuSK) antibodies. MuSK is involved in the formation of clusters of acetylcholine receptors at the endplate.

Both MuSK-related MG and MG associated with acetylcholine receptor antibodies tend to occur in females and can manifest in adolescence. Patients with MuSK-related MG tend to have less ocular involvement then MG patients with acetylcholine receptor antibodies. Patients with MuSK-related MG may present with isolated head drop, facial weakness and atrophy, tongue weakness and atrophy, or weakness of the neck or shoulders. Patients with MuSK-related MG may worsen with edrophonium or develop fasciculations. They may require more aggressive therapy. Rituximab has been used.[23]

**48. C**

Myasthenic crisis is more common during the first few years after diagnosis. Infection, initiation of steroids, a rapid steroid taper, surgery, pregnancy, stress, and certain medications can trigger myasthenic crisis. For example, medications that can trigger MG exacerbation include aminoglycosides, botulinum toxin, immune checkpoint inhibitors, penicillamine, magnesium, and fluoroquinolones.

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Patients who are anti-MuSK antibody positive are at higher risk for myasthenic crisis than patients with acetylcholine binding receptor antibodies.

When a patient is intubated for myasthenic crisis, anticholinesterase medications are withheld to prevent secretions and aspiration.

Myasthenic crisis can be treated with intravenous immunoglobulin (IVIG) or plasmapheresis.

**49. B**

This patient has Lambert-Eaton syndrome (LEMS), which is associated with small cell lung cancers. Patients with LEMS often have antibodies to P/Q-type voltage-gated calcium channels. These interfere with the release of acetylcholine vesicles from the presynaptic nerve terminal. Neuromuscular blocking agents should be avoided in patients with LEMS. Amifampridine is a treatment for LEMS. It is a potassium channel blocker that leads to increased acetylcholine release. Seizures are a contraindication to amifampridine.

**50. B**

Both MG and LEMS are neuromuscular junction disorders. MG is a postsynaptic disorder, and LEMS is a presynaptic disorder. Patients with MG are more likely to present with ocular weakness than patients with LEMS. Patients with LEMS may have an abnormal pupillary response, which is not typical of MG. Patients with LEMS have autonomic dysfunction; dry mouth is a symptom. Patients with LEMS tend to have worse leg weakness than arm weakness, whereas arm weakness is usually worse than leg weakness in MG. Reduced deep tendon reflexes are more likely in LEMS than in MG. Both MG and LEMS show a decrement with 3-Hz repetitive nerve stimulation. However, LEMS shows a significant increment with rapid repetitive nerve stimulation or brief intense exercise; this does not occur in MG. (See Table 16.6.)

*Table 16.6* COMPARISON OF MYASTHENIA GRAVIS AND LAMBERT–EATON SYNDROME

| MYASTHENIA GRAVIS | LAMBERT–EATON SYNDROME |
|---|---|
| **Postsynaptic disorder** | **Presynaptic disorder** |
| **Normal pupillary response, more likely to have ocular weakness** | **May have an abnormal pupillary response** |
| **Arm weakness more likely than leg weakness** | **Leg weakness more likely than arm weakness** |
| **Less likely to have autonomic dysfunction** | **More likely to have autonomic dysfunction such as dry mouth** |
| **Deep tendon reflexes usually normal** | **May have reduced deep tendon reflexes** |
| **Decrement with 3-Hz repetitive nerve stimulation** | **Decrement with 3-Hz nerve stimulation, but there is increment with rapid repetitive nerve stimulation or brief exercise** |

**51.**

1) Axonal
2) Demyelinating

Reduced CMAPs tend to occur in conditions affecting the axon. However, conduction block, which occurs in acquired demyelinating conditions, can cause a decrease in amplitude of the CMAP.

Significantly reduced conduction velocities tend to occur in demyelinating conditions.

**52. A**

A normal hemoglobin A1c level does not rule out DM, which is the most common cause of peripheral neuropathy. A glucose tolerance test is more sensitive.

DM can cause multiple types of neuropathy. A distal symmetric polyneuropathy is common in patients with DM. DM can also cause a small-fiber neuropathy, autonomic neuropathy, oculomotor palsy, mononeuropathies, diabetic amyotrophy, and diabetic neuropathic cachexia.

Diabetic lumbosacral radiculoplexus neuropathy, which is a type of diabetic amyotrophy, can cause significant atrophy of the thigh muscles. It tends to occur in male patients older than age 50 years. It manifests with acute pain in the back, hip, or thigh. This is followed by weakness and atrophy. It is typically asymmetric.

Diabetic neuropathic cachexia also tends to occur in older men with poor glycemic control. Patients have weight loss, truncal dysesthesia, and depression.[24]

The 2022 American Academy of Neurology guideline regarding painful diabetic polyneuropathy (PDN) recommended assessing patients with diabetes for PDN and assessing those with PDN for mood and sleep disturbances. Regarding treatment, opioids should be avoided. Treatment options include tricyclic antidepressants, serotonin–norepinephrine reuptake inhibitors, gabapentinoids, and sodium channel blockers.[25]

**53. D**

This patient has hereditary neuropathy with liability to pressure palsies (HNPP), which is characterized by focal compression neuropathies. Tomacula are seen on nerve biopsy. HNPP is caused by deletion of the *PMP22* gene on chromosome 17. *PMP22* encodes peripheral myelin protein-22.

Mutations in *GDAP1* cause Charcot–Marie–Tooth neuropathy type 4A (CMT4A), which is associated with diaphragm paralysis.

Mutations in *MPZ* and *GJ1B* are discussed below.

**54. D**

Friedreich ataxia is autosomal recessive.

Fabry disease, Kennedy disease, and Charcot–Marie–Tooth neuropathy X (CMTX) are X-linked neuropathies.

**55. C**

This patient has Charcot–Marie–Tooth neuropathy type 1A (CMT1A), which usually manifests with leg weakness and atrophy in the second decade of life. Deep tendon reflexes are decreased, and patients develop foot deformities. Patients with CMT1A who are asymptomatic may develop symptoms when given vincristine. CMT1A is caused by duplication of *PMP22*, whereas HNPP is caused by a deletion in this gene. Both conditions are autosomal dominant.

If the patient has CMT1A phenotype but is negative for *PMP22*, then CMTX may be the diagnosis if there is no male-to-male transmission. CMTX is the X-linked type of CMT. CMT1X is the most common type of CMTX. It is caused by mutations in *GJ1B*, which encodes connexin 32, a gap junction protein.

If the patient has CMT1A phenotype and is negative for *PMP22* but there is male-to-male transmission, then the patient may have CMT1B, which is caused by a mutation in the *MPZ* gene.

Mutations in *MFN2* cause CMT2A, which is an axonal form of CMT. CMT type 1 is demyelinating, CMT type 2 is axonal, CMT type 3 is referred to as Dejerine–Sottas disease, and CMT type 4 is autosomal recessive. CMT2A is usually severe. It manifests in early childhood and is associated with postural tremor and optic atrophy.[26]

Mutations in the gene *RAB7A* cause hereditary sensory and autonomic neuropathy type 1B and CMT2B.

Mutations in the gene *HINT1* cause neuromyotonia and axonal neuropathy.

**56. C**

Friedreich ataxia usually manifests before age 20 years with gait ataxia. Eventually, the cerebellum, corticospinal tracts, posterior columns, spinocerebellar tracts, dorsal root ganglia, and peripheral nerves are all affected. Patients with Friedreich ataxia develop limb and trunk ataxia and dysarthria. The lower extremities become weak, and there is wasting in the hands and feet. Vibration and position sense are lost, and reflexes are reduced. Plantar responses are extensor. Square-wave jerks are a common ocular finding. Sensorineural deafness, diabetes, and cardiac conduction defects may be present.

Large myelinated sensory axons are affected in Friedrich ataxia. Patients with Friedreich ataxia have abnormal sensory NCSs. Compound muscle action potentials are often normal.

Friedreich ataxia is caused by a mutation in the gene *FXN*, which encodes frataxin. Frataxin is an iron-binding protein found in mitochondria. Patients with Friedreich ataxia have an expanded GAA trinucleotide repeat in the *FXN* gene. The gene is on chromosome 9q.

Omaveloxolone, which activates the nuclear factor (erythroid-derived 2)–like 2 (Nrf2) pathway, is a treatment for Friedreich ataxia. Possible side effects include lipid profile abnormalities, elevated liver function tests, and elevated B-type natriuretic peptide (a marker of cardiac function).

**57. D**

This patient has AIDP, which is the most common form of GBS. AIDP is characterized by symmetric, ascending weakness with areflexia. This can progress to quadriparesis and respiratory failure. Measurement of the forced vital capacity and negative inspiratory force can help predict whether the patient is at risk for respiratory failure. Patients can have cardiac arrhythmias and autonomic dysfunction (e.g., sinus tachycardia). Albuminocytologic dissociation is a classic finding in AIDP.

AIDP is immune-mediated. T cells target peripheral nervous system myelin in AIDP. AIDP is usually a postinfectious (or postvaccination) process.

*Campylobacter jejuni* is the illness that most commonly precedes GBS. It is associated with the axonal form of GBS, anti-GM1 antibodies, and a worse prognosis.

Findings that suggest a diagnosis other than GBS include asymmetric weakness, bowel and bladder dysfunction at the onset of symptoms, and a sensory level.[27]

**58. A**

Prolonged F-wave latencies are often the first sign of AIDP on NCSs.

Conduction block and temporal dispersion do occur in acquired demyelinating neuropathies, but prolongation of F-wave latencies usually occurs first.

The sural nerve may be spared in some patients with GBS.

**59. D**

The Miller–Fisher variant of GBS is characterized by the triad of ophthalmoparesis, areflexia, and ataxia. It may present with diplopia.

Bickerstaff brainstem encephalitis is a GBS variant with central nervous system involvement. It is characterized by encephalopathy, ophthalmoparesis, and ataxia. These patients may have hyperreflexia.

Patients with Miller–Fisher syndrome and those with Bickerstaff brainstem encephalitis can have antibodies to GQ1b.

Acute motor axonal neuropathy (AMAN) is an axonal variant of GBS. Facial weakness is less common in AMAN than in AIDP. *Campylobacter jejuni* infection commonly precedes AMAN. The target in AMAN is the nodal and paranodal axolemma, whereas in AIDP it is myelin.

Acute motor-sensory axonal neuropathy (AMSAN) is also an axonal variant of GBS. It has a worse prognosis than AMAN or AIDP. There is axonal damage to the ventral and dorsal roots in AMSAN.

Sensory GBS may be associated with antibodies to GD1b.

Antibodies to GT1a can be seen in GBS patients who present with bulbar palsy.[27,28]

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**60. A**

Botulism, diphtheria, tick paralysis, and porphyria are in the differential diagnosis of GBS.

Botulism causes a descending paralysis. Sensation is normal.

Diphtheria can cause an ascending paralysis. It is caused by an exotoxin produced by *Corynebacterium diphtheriae*. Weakness results from a distal polyneuropathy involving the limbs (a symmetric sensorimotor peripheral neuropathy). An exudate of the throat and trachea is characteristic. Diphtheria causes a palatal neuropathy. In addition to palatal paralysis, other cranial nerves may become involved. Patients may have lack of accommodation with preservation of the light reflex.

Tick paralysis and porphyria also cause an ascending flaccid paralysis.

**61. True**

CIDP causes symmetric proximal and distal weakness. Sensory disturbance is more common in CIDP than in AIDP. Decreased reflexes and albuminocytologic association are seen in CIDP, as in AIDP. Increased CSF white blood cells should raise suspicion for an infectious etiology.

Patients with CIDP have evidence of acquired demyelination similar to that seen in patients with AIDP, such as temporal dispersion, conduction block, increased distal CMAP duration, and prolonged or absent F waves. Similar to patients with AIDP, there may be sural sparing. As in AIDP, T-cell activation is thought to play a role in the pathogenesis of CIDP.

Patients with CIDP should be evaluated for lymphoproliferative disease.

**62. A**

SIDP is an intermediate condition between AIDP and CIDP. (SIDP patients are those who progress for longer than 4 weeks but less than 8 weeks.) AIDP, SIDP, and CIDP are usually symmetric. CSF protein is elevated in SIDP, as in AIDP and CIDP.

Types of chronic acquired demyelinating polyneuropathy include CIDP, distal acquired demyelinating symmetric neuropathy (DADS), MMN, and multifocal acquired demyelinating sensory and motor neuropathy (MADSAM).

Distal acquired demyelinating symmetric neuropathy (DADS) can cause motor or sensory symptoms. Often, it is associated with a monoclonal protein.

MMN causes asymmetric weakness. It tends to begin in the upper extremities in the territory of a specific peripheral nerve. Evidence of demyelination is seen on motor NCSs. Anti-GM1 antibodies may be present.

MADSAM causes asymmetric weakness and sensory loss. Similar to MMN, MADSAM tends to involve the upper extremities first. CSF protein is elevated in MADSAM.[28]

**63. D**

MADSAM is most likely to respond to steroids. It also responds to IVIG.

MMN, AMAN, and AIDP do not respond well to steroids. GBS can be treated with IVIG or plasmapheresis. MMN can be treated with IVIG.

CIDP and SIDP typically respond to steroids.

**64. C**

Immunoglobulin M–monoclonal gammopathy of undetermined significance (IgM-MGUS) is typically associated with a distal large-fiber, sensory-predominant symmetric neuropathy with sensory ataxia. NCSs are consistent with demyelination.

Neuropathy in patients with IgM monoclonal gammopathy is called distal acquired demyelinating symmetric neuropathy with M protein (DADS-M). This is considered a variant of CIDP. However, these patients have more sensory loss and less weakness than most patients with CIDP and are less likely to respond to treatment than those with typical CIDP. Often, patients with DADS-M have antibodies to myelin-associated glycoprotein.

**65. B**

POEMS is a paraneoplastic sensorimotor neuropathy. It is associated with osteosclerotic myeloma. An elevated level of serum vascular endothelial growth factor may be helpful in the diagnosis of POEMS.

Small cell lung cancer can be associated with a sensory neuronopathy (sensory ganglionopathy).

Malignant thymoma can be associated with Morvan syndrome, which is characterized by neuromyotonia, polyneuropathy, limbic encephalitis, and hyperhidrosis. This paraneoplastic condition can be associated with potassium channel antibodies.

Non-Hodgkin lymphoma can be associated with demyelinating neuropathies, such as CIDP.

Hodgkin lymphoma can be associated with anti-Tr antibodies/anti-DNER antibodies and cerebellar degeneration. (DNER is delta/notch-like epidermal growth factor-related receptor.)

**66. A**

This patient has upper and lower motor neuron signs. ALS is the most likely diagnosis. It may begin with weakness and atrophy in a limb or with bulbar signs such as dysphagia.

The El Escorial World Federation of Neurology criteria are used to diagnose ALS. Definite ALS requires upper motor neuron and lower motor neuron signs in three of four regions (bulbar, cervical, thoracic, and lumbosacral regions).[29]

Primary lateral sclerosis only affects the upper motor neurons.

Progressive muscular atrophy and spinal muscular atrophies affect the lower motor neurons. Other motor

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neuron diseases include X-linked spinal bulbar muscular atrophy, monomelic amyotrophy, poliomyelitis, and West Nile virus poliomyelitis.

**67. D**

Spasticity is the condition most likely to be seen in early ALS. Autonomic disturbance, incontinence, ophthalmoplegia, movement disorders, and sensory abnormalities should raise concern for a diagnosis other than ALS.

ALS is the most common acquired motor neuron disease. However, there are familial forms. The most common genetic cause of ALS is mutations in *C9orf72*. An expansion of a hexanucleotide repeat in the gene *C9orf72* causes familial ALS and familial frontotemporal dementia. Mutations in the gene encoding superoxide dismutase also cause familial ALS. Mutations in *TARDBP* and *FUS* are less common causes of familial ALS (see Box 16.3).

### *Box 16.3* GENES THAT ARE MUTATED IN FAMILIAL AMYOTROPHIC LATERAL SCLEROSIS

- *C9orf72*
- *SOD1*
- *TARDBP*
- *FUS*

**68. B**

The goal of riluzole is to slow ALS progression. Riluzole inhibits glutamate release. It can decrease appetite and raise liver function tests.

Percutaneous endoscopic gastrostomy and noninvasive ventilation may prolong survival in patients with ALS.[30]

**69. A**

This patient has Kennedy disease, which is also known as X-linked spinobulbar muscular atrophy. It is a motor neuron disease caused by mutations in the gene *AR*, which encodes the androgen receptor. Patients with Kennedy disease have an expanded number of CAG repeats in the gene. Clinical findings include progressive bulbar and extremity weakness. Tongue and perioral fasciculations are characteristic features. Androgen insensitivity causes gynecomastia, infertility, and impotence. Patients are at increased risk for diabetes mellitus (DM).

**70. C**

This patient has SMA. Most patients with SMA have homozygous deletions of exon 7 or exons 7 and 8 in *SMN1*, which interferes with production of survival motor neuron protein. Reduced expression of survival motor protein ultimately leads to injury of α-motor neurons in the spinal cord and brainstem. This causes progressive weakness of extremity, trunk, bulbar, and respiratory muscles and muscle atrophy. Historically, EMG/NCS and muscle biopsy were used in the diagnosis, but genetic testing is now preferred.[31]

Mutations in *SMN1* on chromosome 5q are the most common cause of SMA. *SMN1* and *SMN2* both encode for survival motor neuron protein, but *SMN1* produces more functional protein. *SMN2* is adjacent to *SMN1* and modifies the severity of SMA; more copies of *SMN2* result in less severe disease.

Most patients with SMA type 1 have two copies of the *SMN2* gene. Without treatment, most patients with SMA type 1 never sit independently and die or require ventilation by 13.5 months on average.[32] There is urgency to treat patients with two copies of *SMN2* before symptom onset.[31]

Treatments for SMA include nusinersen, risdiplan, and onasemnogene abeparovec-xioi. Nusinersen is an *SMN-2* directed antisense oligonucleotide delivered intrathecally. It increases exon 7 inclusion in *SMN2* messenger ribonucleic acid (mRNA) transcripts and increases production of full-length survival motor neuron protein. Specifically, it binds to an intronic splice silencer site in intron 7, causing splice-switching.[31] There is a risk for renal toxicity (including fatal glomerulonephritis), thrombocytopenia, and coagulation abnormalities.[33]

Risdiplam is a survival of motor neuron 2-directed RNA splicing modifier.[21]Similar to nusinersen, risdiplam increases exon 7 inclusion in *SMN2* mRNA transcripts and production of full-length survival motor neuron protein.[34]However, risdiplam has a different mechanism of action and is given orally rather than intrathecally. Specifically, risdiplam binds to two sites in the *SMN2* pre-mRNA.[31]

Onasemnogene abeparovec-xioi is an intravenous adeno-associated virus (AAV) vector-based gene therapy that delivers an *SMN1* gene to the motor neurons. (The AAV9 serotype can cross the blood–brain barrier.)[35] There is a risk for liver failure.[36](See Table 16.7.)

### *Table 16.7* TREATMENTS FOR SPINAL MUSCULAR ATROPHY

| MEDICATION | BENEFIT | MECHANISM OF ACTION |
|---|---|---|
| **Nusinersen** | **Increases exon 7 inclusion in *SMN2* mRNA transcripts** | **Anti-sense oligonucleotide, binds to an intronic splice silencer site in intron 7 of *SMN2* pre-mRNA** |
| **Risdiplam** | **Increases exon 7 inclusion in *SMN2* mRNA transcripts** | ***SMN2*-directed RNA splicing modifier, binds to two sites in the *SMN2* pre-mRNA** |
| **Onasemnogene abeparovec-xioi** | **Delivers an *SMN1* gene to the motor neurons** | **Vector-based gene therapy** |

DNA methylation analysis is helpful in identifying patients with Prader–Willi syndrome but would not be helpful in diagnosing SMA.

**71. B**

Chloroquine can cause a demyelinating neuropathy.

Amiodarone, lithium, metronidazole, nitrofurantoin, and vinka alkaloids can cause axonal neuropathy.

**72. B**

This is monomelic amyotrophy, also known as Hiriyama disease. A cervical collar is recommended, and prolonged forward neck flexion should be avoided.[37]

Patients with Kennedy disease, which is also known as X-linked spinobulbar muscular atrophy, may have low levels of insulin-like growth factor 1.[37]

Cytoplasmic TDP-43 inclusions occur in ALS. Mutations in the *TARDBP* gene, which encodes TDP-43, are a cause of familial ALS.

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# 17.

# NEURO-ONCOLOGY

Please note: The 2021 World Health Organization (WHO) Classification of Tumours of the Central Nervous System was used for this chapter.

## QUESTIONS

1. **A 28-year-old woman who presents with headache and vomiting is diagnosed with a brain tumor in the emergency department. Computed tomography (CT) indicates a mass effect. Which of the following is recommended to be done first?**
   A. Start an anti-seizure medication (ASM), preferably one that is not an enzyme inducer.
   B. Start dexamethasone.
   C. Start temozolomide.
   D. Order a magnetoencephalography (MEG) scan.

2. **True or false?**
   In the 2021 WHO Classification of Tumours of the Central Nervous System, tumor grade is determined solely on histology.

3. **What are the two most common brain tumors of childhood?**
   A. Medulloblastoma and pilocytic astrocytoma
   B. Ependymoma and germinoma
   C. Oligodendroglioma and ganglioglioma
   D. Schwannoma and meningioma

4. **Which of the following statements is *false*?**
   A. Most primary brain tumors are glial tumors.
   B. Brain metastases are less common than primary brain tumors.
   C. Seizures are a common presenting symptom of low-grade gliomas.
   D. Risk factors for primary brain tumors include ionizing radiation and immunosuppression.

5. **An 18-year-old woman presents with seizures. Magnetic resonance imaging (MRI) shows a cyst with an enhancing nodule in the temporal lobe. Eosinophilic granular bodies and pilocytic cells are seen on histopathology. What is the most likely diagnosis?**
   A. Craniopharyngioma—adamantinomatous type
   B. Dysembryoplastic neuroepithelial tumor (DNET)
   C. Ganglioglioma
   D. Meningioma

6. **Which of the following inherited cancer syndromes is *least* likely to be associated with medulloblastoma?**
   A. Gorlin syndrome
   B. Li–Fraumeni syndrome
   C. Turcot syndrome
   D. Cowden syndrome (multiple hamartoma syndrome)

7. **A large number of patients with dysplastic gangliocytoma of the cerebellum (Lhermitte–Duclos disease) have which of the following syndromes?**
   A. Cowden syndrome (multiple hamartoma syndrome)
   B. Gorlin syndrome
   C. Von Hippel–Lindau disease
   D. Von Recklinghausen disease

8. **Which of the following is *least* likely to be the cause of an intraventricular tumor?**
   A. Subependymal giant cell astrocytoma
   B. Central neurocytoma
   C. Subependymoma
   D. Paraganglioma

9. **Which of the following statements is *false*?**
   A. Oligodendrogliomas are characterized by cells with a "fried egg" appearance, microcalcifications, and branching capillaries.
   B. Oligodendrogliomas have a tendency to bleed.
   C. Patients with oligodendrogliomas frequently present with seizures.
   D. Oligodendrogliomas most commonly occur in the temporal lobe.

10. **Fill in the blank: Meningiomas arise from __________________.**
    A. Dura cells
    B. Arachnoid cells
    C. Pia cells

11. **Which of the following is *not* a characteristic of meningiomas?**
    A. Whorls are present.
    B. Psammoma bodies are present.
    C. Desmosomes are present.
    D. They stain with epithelial membrane antigen (EMA).
    E. They stain with Congo red.

12. **Which of the following is *not* characteristic of low-grade meningiomas?**
    A. Brain invasion
    B. Bone hyperostosis

C. Dural tail
D. Uniform enhancement

**13. Which of the following cancers is *least* likely to spread to the brain?**
A. Breast
B. Gastrointestinal
C. Melanoma
D. Prostate
E. Renal

**14. Which of the following cancers is *least* likely to cause hemorrhagic metastases?**
A. Choriocarcinoma
B. Gastrointestinal
C. Melanoma
D. Renal

**15. A 20-year-old man presents with an intraventricular tumor, which is resected. On light microscopy, it resembles an oligodendroglioma but stains positively for synaptophysin. Which of the following tumors fits this description?**
A. Central neurocytoma
B. Gangliocytoma
C. Ganglioneuroblastoma
D. Ganglioglioma

**16. Which of the following is a tumor of the filum terminale that mimics an ependymoma with pseudorosettes but is positive for synaptophysin and chromogranin?**
A. Astroblastoma
B. Paraganglioma of the filum terminale
C. Gangliocytoma
D. Ganglioneuroblastoma

**17. A 7-year-old boy undergoes surgery for a medulloblastoma in the cerebellum. On postoperative day 2, dysarthria is noted. This worsens, and then he stops speaking altogether. What is this syndrome?**
A. Posterior fossa syndrome
B. Broca aphasia
C. Transcortical motor aphasia
D. Selective mutism

**18. A 23-year-old woman presents with a mass that appears to be a cyst with an enhancing mural nodule. The mass is *least* likely to be which of the following tumors?**
A. Ganglioglioma
B. Hemangioblastoma
C. Meningioma
D. Pilocytic astrocytoma
E. Pleomorphic xanthoastrocytoma

**19. What is the most common pineal tumor?**
A. Germinoma
B. Pineoblastoma
C. Pineocytoma
D. Astrocytoma

**20. Mutations in which chromosome are associated with neurofibromas, schwannomas, meningiomas, and atypical teratoid/rhabdoid tumor (AT/RT)?**
A. Chromosome 3
B. Chromosome 11
C. Chromosome 17
D. Chromosome 22

**21. This type of tumor manifests with seizures in children, often in the temporal lobe. It is low grade and resembles an oligodendroglioma microscopically but has a mucinous component in which neurons seem to float. There may be accompanying cortical dysplasia. This tumor is which of the following?**
A. Central neurocytoma
B. Craniopharyngioma—adamantinomatous type
C. Desmoplastic infantile astrocytoma
D. Dysembryoplastic neuroepithelial tumor
E. Ganglioglioma

**22. Which abnormality is most likely to be found in a pilocytic astrocytoma?**
A. H3K27 alteration
B. Defect in the mammalian target of rapamycin (mTOR) pathway
C. Defect in the mitogen-activated protein kinase (MAPK) signaling pathway
D. Defect in SHH signaling
E. *TP53* mutation

**23. A 30-year-old receiving chemotherapy develops vomiting, headache, and seizures. She is found to have a sagittal sinus thrombosis. Which of the following medications is most likely responsible?**
A. L-Asparaginase
B. Busulfan
C. Chlorambucil
D. Cytarabine
E. Ifosfamide

**24. Which of the following statements is *false*?**
A. Most primary central nervous system (CNS) lymphomas are B-cell lymphomas.
B. Primary CNS lymphoma responds well to steroids but recurs.
C. Primary CNS lymphoma can resemble glioblastoma on MRI.
D. Primary CNS lymphoma always occurs as a single, localized lesion.
E. Primary CNS lymphoma is characterized by perivascular cuffing, which can be seen with reticulin stain.

**25. Which of the following is *least* likely to be seen in a patient with a hypothalamic hamartoma?**
A. Behavioral problems
B. Gelastic seizures
C. Precocious puberty
D. Metastases

**26. Chemical meningitis can occur if there is leakage from which type of cyst?**

A. Colloid cyst
B. Epidermoid cyst
C. Neurenteric cyst
D. Rathke's cleft cyst

**27. Which of the following tumors arises from small nests of cells in the sacrum and clivus?**
A. Chordoma
B. Choriocarcinoma
C. Craniopharyngioma
D. Atypical teratoid/rhabdoid tumor

**28. Which of the following findings predicts a better prognosis in gliomas?**
A. Epidermal growth factor receptor (EGFR) amplification
B. Mutation in isocitrate dehydrogenase 1 and 2
C. *N-Myc* gene amplification
D. Telomerase reverse transcriptase (TERT) promoter mutation

**29. A 24-year-old man is referred by his primary care physician for a pituitary mass found on MRI. Which visual field defect might be present?**
A. Bitemporal hemianopsia
B. Binasal hemianopsia
C. Homonymous hemianopsia

**30. Which of the following is the most common pituitary lesion?**
A. Pituitary adenoma/pituitary neuroendocrine tumor
B. Pituitary carcinoma
C. Lymphocytic hypophysitis
D. Metastasis

**31. Which of the following is the most common type of pituitary adenoma?**
A. Adrenocorticotropic hormone–secreting tumor
B. Growth hormone–secreting tumor
C. Prolactinoma
D. Thyroid-stimulating hormone–secreting tumor

**32. A 25-year-old man is found to have a prolactinoma. On examination, he has a visual field defect. Which of the following is the first-line treatment?**
A. Surgery
B. Radiation
C. Chemotherapy
D. Bromocriptine

**33. Which of the following is *least* likely to be found in the lumbar cistern?**
A. Schwannoma
B. Meningioma
C. Central neurocytoma
D. Myxopapillary ependymoma
E. Paraganglioma of the filum

**34. A 2-year-old presents with chaotic eye movements and quick jerks of the extremities. Which of the following tumors is most likely?**
A. Ependymoma
B. Germinoma
C. Medulloblastoma
D. Neuroblastoma

**35. A 2-year-old is found to have a brain tumor, which is resected. The tumor has small blue cells, similar to medulloblastoma, and stains positive for vimentin. There is a mutation of *SMARCB1* (also known as *INI1/hSNF5/BAF47*) on chromosome 22. Which of the following tumors is most likely?**
A. AT/RT
B. Desmoplastic infantile astrocytoma
C. CNS neuroblastoma
D. Polymorphous low-grade neuroepithelial tumor of the young (PLNTY)

**36. A 55-year-old woman presents with seizures. MRI shows an enhancing lesion involving the corpus callosum in a butterfly pattern. Biopsy shows necrosis with pseudopalisading and microvascular proliferation. What is the most likely diagnosis?**
A. Glioblastoma multiforme, isocitrate dehydrogenase (IDH)-wildtype
B. Pleomorphic xanthoastrocytoma
C. Lymphoma
D. AT/RT

**37. Which of the following is *not* associated with prominent numbers of eosinophilic granular bodies?**
A. Ganglioglioma
B. Pilocytic astrocytoma
C. Pleomorphic xanthoastrocytoma
D. Subependymoma

**38. Subependymal giant cell astrocytomas (SEGAs) are associated with which disease?**
A. Ataxia–telangiectasia
B. Neurofibromatosis type 1
C. Tuberous sclerosis complex (TSC)
D. Von Hippel–Lindau disease

**39. A 25-year-old with testicular cancer presents with up-gaze weakness, limbic encephalitis, and cataplexy. Which of the following is most likely to be found?**
A. CASPR2 autoantibodies
B. Dipeptidyl-peptidase-like protein 6 (DPPX) autoantibodies
C. Immunoglobulin-like cell adhesion molecule 5 (IgLON5) autoantibodies
D. Ma2 autoantibodies
E. mGlu receptor 5 autoantibodies

**40. True or false?**
Areas of necrosis can be seen in low-grade ependymomas.

**41. A 16-year-old boy presents with difficulties riding his skateboard. MRI shows a cyst with a mural nodule in the cerebellum. The tumor is resected, and Rosenthal fibers, eosinophilic granular bodies, microcysts, and long bipolar cytoplasmic cell processes are seen. What is the most likely diagnosis?**

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A. Ependymoma
B. Hemangioblastoma
C. Medulloblastoma
D. Pilocytic astrocytoma

**42. True or false?**
Carcinomatous meningitis and lymphomatous meningitis can be associated with very low glucose levels, similar to bacterial meningitis.

**43. Which of the following statements is *false*?**
A. In the familial form of retinoblastoma, one copy of the tumor suppressor *Rb* gene is inactivated in the germ line.
B. Patients with familial retinoblastoma are at increased risk for melanoma.
C. A patient with bilateral retinoblastomas and an osteosarcoma has trilateral retinoblastoma.
D. Flexner–Wintersteiner rosettes can be seen in retinoblastoma.

**44. A 30-year-old woman presents with seizures and altered mental status. Extreme delta brushes are seen on her electroencephalogram. She is eventually diagnosed with anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis. Which of the following tumors is most closely associated with this diagnosis?**
A. Breast cancer
B. Pituitary adenoma
C. Cervical cancer
D. Ovarian teratoma

**45. Which of the following antibodies can cause pseudo-obstruction syndrome?**
A. Anti-Hu/ANNA-1
B. Anti-Ri/ANNA-2
C. Anti-Yo
D. Anti-Tr/DNER

**46. Which of the following types of antibodies cause Lambert–Eaton myasthenic syndrome?**
A. Antibodies to the α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptor
B. Antibodies to P/Q-type voltage-gated calcium channels
C. Antibodies to voltage-gated potassium channels
D. Antibodies to the metabotropic glutamate receptor subtype 1 (mGluR1)
E. Antibodies to leucine-rich, glioma-inactivated 1 (LGI1) protein

**47. A 20-year-old man presents with decreased hearing and unsteadiness. MRI shows mass lesions in the internal auditory canals bilaterally. Pathology shows Antoni A and Antoni B patterns and Verocay bodies.**
**a. What are these lesions?**
A. Ependymomas
B. Schwannomas
C. Meningiomas
D. Central neurocytomas

**b. Which of the following diagnoses should be considered?**
A. TSC
B. Neurofibromatosis type 1
C. Neurofibromatosis type 2/NF2-related schwannomatosis
D. Ménière disease

**48. Which of the following medications is most likely to cause chronic encephalopathy?**
A. Cyclosporin
B. Etoposide
C. Ifosfamide
D. Methotrexate
E. Tamoxifen

**49. A patient develops severe weakness after one dose of vincristine. Which of the following is the most likely cause?**
A. The patient has Charcot–Marie–Tooth disease.
B. The patient is a child.
C. The patient is taking carbamazepine.
D. The patient is taking phenytoin.

**50. Which of the following statements about cancer therapies is *false*?**
A. Cerebral radiation necrosis can resemble tumor recurrence.
B. Radiation can cause brain tumors and stroke.
C. Peripheral neuropathy due to chemotherapy always improves after discontinuation of treatment.
D. BRAF inhibitors can cause paradoxical stimulation of tumor growth in pediatric low-grade astrocytoma with the *KIAA1549-BRAF* truncation/fusion alteration.

**51. Which of the following is a monoclonal antibody to vascular endothelial growth factor (VEGF) that helps to restore the blood–brain barrier?**
A. Anakinra
B. Bevacizumab
C. Ibrutinib
D. Ipilimumab
E. Tocilizumab

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# NEURO-ONCOLOGY

## ANSWERS

**1. B**

The first step is to start dexamethasone, which treats vasogenic edema.

ASMs are not recommended for prevention of the first seizure.[1] If an ASM is indicated, enzyme-inducing ASMs should be avoided because they can affect the metabolism of chemotherapy drugs and steroids. Levetiracetam would be a better option.

Temozolomide is a treatment for brain tumors, but it is not the first step.

A MEG scan may be helpful later for surgical planning, but it does not need to be done first.

**2. False**

Molecular genetics play a role in the 2021 WHO classification of brain tumors. For example, an IDH-mutant diffuse astrocytic tumor with *CDKN2A/B* homozygous deletion results in a CNS WHO grade of 4, even if there is no microvascular proliferation or necrosis.[2]

Also, tumor grading nomenclature was changed. Arabic numbers are used instead of Roman numbers, and tumors are graded within their type. The term "anaplastic" no longer implies WHO grade 3 (formerly III).[2]

See Box 17.1 regarding additional changes in terminology.

### *Box 17.1* TERMS NO LONGER IN USE IN NEURO-ONCOLOGY

- Anaplastic astrocytoma
- Anaplastic oligodendroglioma
- Gliomatosis cerebri
- Pediatric glioblastoma
- Primitive neuroectodermal tumor (PNET)

**3. A**

Medulloblastoma and pilocytic astrocytoma are the two most common brain tumors of childhood.

**4. B**

Brain metastases are more common than primary brain tumors. Brain metastases are most often found at the cerebral gray–white junction.

**5. C**

This patient has a ganglioglioma.

Gangliogliomas, hemangioblastomas, pilocytic astrocytomas, and pleomorphic xanthoastrocytomas have the appearance of a cyst with an enhancing mural mass.

Gangliogliomas, pilocytic astrocytomas, and pleomorphic xanthoastrocytomas have eosinophilic granular bodies.

Craniopharyngiomas typically occur in the sellar region. There may be a cystic component, which may be filled with "machine oil–like" fluid. The histopathology of adamantinomatous craniopharyngioma is characterized by "wet keratin." There are cords of squamous epithelial cells. Calcifications are common. Adamantinomatous craniopharyngioma is associated with *CTNNB1* mutations, and papillary craniopharyngioma is associated with *BRAF* mutations.[2]

**6. D**

Medulloblastoma is seen in Gorlin, Li–Fraumeni, and Turcot syndromes.

Cowden syndrome is characterized by multiple hamartomas. It is autosomal dominant, and there is also a high risk of developing breast cancer or thyroid cancer. There is a germline mutation in the tumor suppressor gene *PTEN* on chromosome 10q23.

Gorlin syndrome is nevoid basal cell carcinoma syndrome, which is associated with an increased risk for medulloblastomas and meningiomas. It is autosomal dominant and is most often caused by a germline mutation in the Patched gene (*PTCH*) on chromosome 9q22. It manifests with developmental anomalies such as macrocephaly, dural calcifications, jaw cysts, and rib abnormalities.

Li–Fraumeni syndrome is caused by a *TP53* (a tumor suppressor) germline mutation, which results in multiple neoplasms such as breast cancer, sarcoma, and brain tumors including astrocytoma, medulloblastoma, choroid plexus carcinoma, and ependymoma.

Turcot syndrome is associated with a familial adenomatous polyposis mutation on the *APC* tumor suppressor gene (chromosome 5q21). Patients can have many polyps in the colon and are at risk for brain tumors such as medulloblastoma, malignant glioma, and ependymoma.

See Table 17.1to review genetic mutations associated with familial tumor syndromes.

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*Table 17.1* GENE MUTATIONS ASSOCIATED WITH FAMILIAL TUMOR SYNDROMES

| FAMILIAL TUMOR SYNDROME | MUTATED GENE |
|---|---|
| **Cowden syndrome** | *PTEN* |
| **Gorlin syndrome** | *PTCH, SUFU* |
| **Li–Fraumeni syndrome** | *TP53* |
| **Neurofibromatosis type 1** | *NF1* |
| **Neurofibromatosis type 2/NF2-related schwannomatosis** | *NF2* |
| **Schwannomatosis** | *SMARCB1, LZTR1* |
| **Tuberous sclerosis complex** | *TSC1, TSC2* |
| **Turcot syndrome** | *APC* |
| **Von Hippel–Lindau disease** | *VHL* |

**7. A**

A significant number of patients with dysplastic gangliocytoma of the cerebellum (Lhermitte–Duclos disease) have Cowden syndrome (multiple hamartoma syndrome), which is caused by a germline *PTEN* mutation.

Gorlin syndrome is nevoid basal cell carcinoma syndrome. Patients have an increased risk for medulloblastoma.

Von Hippel–Lindau disease is associated with hemangioblastomas in the cerebellum.

Von Recklinghausen disease is another name for neurofibromatosis type 1 (NF type 1). NF type 1 is caused by mutations in the gene *NF1*, which is found on chromosome 17. The gene *NF1* encodes for neurofibromin, which regulates Ras signaling; therefore, NF type 1 is classified as a RASopathy.

**8. D**

The differential diagnosis of an intraventricular tumor includes subependymal giant cell astrocytomas, which are found in TSC; central neurocytoma; choroid plexus papilloma and carcinoma; ependymoma; and subependymoma. Intraventricular meningiomas are rare but can occur.

Paragangliomas are neuroendocrine tumors that are thought to arise from neural crest cells associated with autonomic ganglia. It is uncommon for paragangliomas to occur in the CNS, but when they are present, they tend to occur in the cauda equina region and are intradural.

**9. D**

Oligodendrogliomas are diffusely infiltrating gliomas. They typically occur in the cerebral hemispheres, most often in the frontal lobe.

**10. B**

Meningiomas arise from arachnoid cells. In general, they are more common in women than in men and tend to occur in older patients. Risk factors include ionizing radiation and hereditary tumor syndromes such as neurofibromatosis type 2/NF2-related schwannomatosis. Meningiomas may enlarge during pregnancy.

**11. E**

Congo red stains amyloid.

Meningiomas typically stain positive for vimentin and EMA. On light microscopy, whorls or psammoma bodies may be seen. There may be calcification or cysts. Desmosomal intercellular junctions are seen on electron microscopy.

**12. A**

Brain invasion is not characteristic of low-grade meningiomas.

Meningiomas are dural-based tumors. A “dural tail” may be seen on MRI. Most meningiomas are circumscribed, are isodense on MRI, and homogenously enhance with contrast. There may be hyperostosis of the overlying bone. Seizure is a common presenting symptom, and angiography shows a “sunburst effect” or “blushing” with large dural arteries.

Meningiomas with *CDKN2A/B* mutations are considered WHO grade 3.[2]

**13. D**

Of the cancers listed, prostate cancer is least likely to metastasize to the brain. Similarly, cervical cancer rarely metastasizes to the brain. Breast, gastrointestinal, lung, and renal cancers, as well as melanoma, are more likely to spread to the brain.

**14. B**

Of those listed, gastrointestinal cancers are least likely to cause hemorrhagic metastases. Choriocarcinoma, melanoma, and renal cancers are more likely to cause hemorrhagic metastases. Metastases with the highest risk of bleeding include lung, melanoma, renal, choriocarcinoma, and thyroid cancer. Lung cancer causes the highest proportion of hemorrhagic metastases, but melanoma and choriocarcinoma have the highest relative incidence.

**15. A**

Central neurocytoma resembles an oligodendroglioma but stains positively for synaptophysin and is found in the ventricles.

**16. B**

Paraganglioma of the filum terminale is an oval or sausage-shaped neuroendocrine tumor of the filum terminale. Per the 2021 WHO Classification of Tumors of the Central Nervous System, it is considered a nerve tumor.[2] On MRI, serpentine vessels may be seen. On histopathology, this tumor mimics an ependymoma with pseudorosettes but stains positive for synaptophysin and chromogranin.

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**17. A**

This patient has posterior fossa syndrome, which is otherwise known as cerebellar mutism. It can occur in patients, especially children, who have undergone posterior fossa surgery.

**18. C**

Gangliogliomas, hemangioblastomas, pilocytic astrocytomas, and pleomorphic xanthoastrocytomas have the appearance of a cyst with an enhancing mural mass.

Gangliogliomas are located throughout the CNS (i.e., brain, optic nerve, pituitary, pineal gland, and spinal cord), but the majority are in the temporal lobe.

Hemangioblastomas are located in the cerebellum.

Pilocytic astrocytoma (CNS WHO grade 1) is the most common type of glioma in children, and most occur in the cerebellum. The most common pediatric supratentorial site is the optic pathway/hypothalamus.

Pleomorphic xanthoastrocytoma is typically in a superficial location over the meninges and cerebrum, mostly supratentorial, and especially in the temporal lobes.

**19. A**

The most common pineal tumor is the germinoma, which is a germ cell tumor. Germinomas are radiosensitive and have a good prognosis. Germinomas stain with placental alkaline phosphatase. Pure germinomas are most common in the pineal region.

Other germ cell tumors (nongerminomas) include choriocarcinomas (which stain with human chorionic gonadotropin), embryonal carcinomas, yolk sac or endodermal sinus tumors (which stain with α-fetoprotein), teratomas, and mixed germ cell tumors.

**20. D**

Mutations in chromosome 22 are found in meningiomas, ependymomas, neurofibromas, schwannomas, and AT/RTs (see Box 17.2).

*Box 17.2* **TUMORS ASSOCIATED WITH CHROMOSOME 22 DELETIONS**

- Atypical teratoid/rhabdoid tumors
- Ependymomas
- Meningiomas
- Neurofibromas
- Schwannomas

Chromosome 22 deletions are common in meningiomas. Mutations in the *NF2* gene (at chromosome 22q12.2) are frequent. The *NF2* gene encodes for the protein merlin. The mutations can be seen in patients without neurofibromatosis.

Mutations in v-akt murine thymoma viral oncogene homolog 1 (*AKT1*) and in smoothened, frizzled class receptor (*SMO*) have been found in some meningiomas. AKT1 regulates the phosphatidylinositol 3-kinase pathway, and SMO is a component of the hedgehog pathway.[3]

**21. D**

Dysembryoplastic neuroepithelial tumor (DNET) is a low-grade glioneuronal tumor that is prone to causing seizures. There may be accompanying cortical dysplasia. DNET is most commonly found in the temporal lobe. Imaging may show multiple nodules. There also may be molding of overlying bone. Its microscopic features include oligodendroglioma-like cells and neurons that appear to be floating. Some cases are associated with *FGFR1* mutations. This tumor is primarily treated with resection.

**22. C**

Pilocytic astrocytoma is most likely to be associated with a defect in the MAPK signaling pathway, such as mutations in *RAS*, *BRAF*, or *MEK*. A common mutation in pilocytic astrocytoma is the *KIAA1549-BRAF* fusion. Mutations in *NF1* also cause pilocytic astrocytoma. MAPK pathway alterations can also be found in other tumors, including some cases of polymorphous low-grade neuroepithelial tumor of the young.[2]

H3K27 alterations occur in diffuse midline glioma, one of the pediatric-type diffuse high-grade gliomas.[2] These tumors have a poor prognosis and contribute significantly to brain tumor-related deaths in children.[4] Diffuse intrinsic pontine glioma (DIPG) is one of the diffuse midline gliomas and can be associated with H3K27 alterations. DIPG tumors can encase the basilar artery and currently have no cure.[4]

TSC is associated with upregulation of the mTOR pathway. Inhibitors of mTOR are sometimes used to treat tumors and epilepsy associated with TSC.

The molecularly defined medulloblastomas include WNT-activated, SHH-activated and *TP53*-wildtype, SHH-activated and *TP53*-mutant, and non-WNT/non-SHH.

**23. A**

L-Asparaginase can cause cerebral venous thrombosis due to antithrombin III deficiency. It can also cause altered mental status.

Busulfan, chlorambucil, and ifosfamide can cause seizures but are less likely to result in a sagittal sinus thrombosis.

Cytarabine can cause a cerebellar syndrome, encephalopathy, and aseptic meningitis (if given intrathecally).

**24. D**

Primary CNS lymphoma is diffuse and demonstrates homogeneous enhancement. There can be multiple lesions. The spinal cord, the cerebrospinal fluid (CSF), or the eye may be involved. Primary CNS lymphoma can occur in immunocompetent individuals but is more

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common in immunocompromised individuals, such as patients with HIV or Epstein–Barr virus infection. Most commonly, primary CNS lymphomas are diffuse, large B-cell lymphomas. Cells tend to have an angiocentric arrangement. CNS lymphoma is treated with chemotherapy (e.g., methotrexate) and radiation. These tumors are very responsive to steroids but recur. Biopsy is recommended before steroids are given.

**25. D**

Hypothalamic hamartomas are associated with behavioral problems, gelastic seizures, and precocious puberty. They are non-neoplastic and do not metastasize.

**26. B**

If an epidermoid or dermoid cyst leaks, chemical meningitis can occur. Dermoid tumors contain hair follicles and sebaceous glands, are located in the midline, manifest earlier in life, and produce oily secretions. Epidermoid tumors are most common in the cerebellopontine angle cistern, followed by the parasellar and suprasellar regions. They contain keratin and cholesterol crystals.

Neurenteric cysts tend to occur in the spinal canal and are thought to be derived from respiratory/gastrointestinal tract remnants.

Rathke's cleft cysts occur between the anterior and posterior lobes of the pituitary gland and are thought to arise from remnants of the pharyngeal epithelial pouch.

**27. A**

Chordomas are invasive tumors that arise from notochord remnants in the clivus and sacrum.

Choriocarcinomas are a type of germ cell tumor.

Craniopharyngioma is an epithelial tumor in the sellar region that is thought to arise from Rathke's pouch epithelium.

AT/RTs are most commonly found in the cerebellum but can occur in the cerebrum.

**28. B**

In the fifth edition of the WHO Classification of Tumours of the Central Nervous System, common adult-type diffuse gliomas are divided into three types: astrocytoma, IDH-mutant; oligodendroglioma, IDH-mutant and 1p/19q-codeleted; and glioblastoma, IDH-wildtype.[5] Gliomas with mutations in isocitrate dehydrogenase 1 (IDH1) and IDH2 tend to have a better prognosis than glioblastoma multiforme, IDH-wildtype. Patients with gliomas with mutations in IDH1 and IDH2 often present with seizures.[6]

IDH-wildtype diffuse astrocytoma with EGFR amplification, TERT promotor mutation, or +7/−10 copy number changes can be designated as glioblastoma, IDH-wildtype CNS WHO grade 4, even if the histology is consistent with a lower grade.[5]

Methylation of the $O^6$-methylguanine–DNA methyltransferase (MGMT) promoter affects prognosis in glioblastoma multiforme. If MGMT is methylated, then the tumor is more susceptible to alkylating chemotherapy agents such as temozolomide and is associated with better overall survival.

**29. A**

Of the options listed, a pituitary mass is most likely to cause bitemporal hemianopsia.

**30. A**

Of the lesions mentioned, pituitary adenoma/pituitary neuroendocrine tumor is the most common.

Pituitary adenomas typically arise from the anterior pituitary. Microadenomas are smaller than 10 mm in diameter, and macroadenomas are larger than 10 mm.

Pituitary apoplexy, which is characterized by hemorrhagic necrosis of the pituitary, can occur in some cases of pituitary tumor. Symptoms include headache, lethargy, and increased intracranial pressure.

A pituitary carcinoma may be a metastasis, especially from lung or breast cancer.

Lymphocytic hypophysitis is characterized by infiltration of the pituitary by lymphocytes. It can occur in association with pregnancy or shortly after delivery. It can cause diabetes insipidus (DI).

Langerhans histiocytosis also occurs in the suprasellar/pituitary region and can cause DI.

**31. C**

The most common type of pituitary adenoma is prolactinoma.

**32. D**

Dopamine agonists such as bromocriptine are first-line treatment for prolactinomas, even if the patient has a visual field defect. However, if the lesion does not respond quickly, surgery is considered.

Dopamine inhibits prolactin-secreting pituitary cells. Dopamine agonists decrease prolactin production and decrease the size of the tumor.

**33. C**

Schwannomas, meningiomas, myxopapillary ependymomas, and paragangliomas of the filum terminale can be found in the lumbar cistern.

Central neurocytoma is an intraventricular tumor.

**34. D**

This patient has opsoclonus–myoclonus–ataxia syndrome, which is a paraneoplastic syndrome seen in patients with neuroblastoma. *N-myc* amplification, late age at onset, diploidy, and reduced catecholamine metabolite production are associated with poor prognosis.

In children, opsoclonus–myoclonus–ataxia syndrome may be associated with ANNA-1/anti-Hu antibodies. In

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adults, opsoclonus–myoclonus–ataxia syndrome is more likely to be associated with ANNA-2/anti-Ri antibodies in the setting of breast or lung cancer.

**35. A**

This patient has AT/RT. AT/RT is a high-grade malignant tumor that usually manifests in children younger than age 3 years but can occur in adults. It can occur anywhere in the neuroaxis. Like medulloblastoma, AT/RT is a type of CNS embryonal tumor and has small blue cells. In AT/RT, rhabdoid cells are present, and the tumor stains positive for vimentin. Most of the tumors are associated with a mutation in *SMARCB1* (which is also known as *INI1*, *hSNF5*, or *BAF47*) on chromosome 22. Less often, AT/RTs are due to mutations in *SMARCA4* (also known as *BRG1*).[5]

**36. A**

This patient has glioblastoma, IDH-wildtype.

The butterfly pattern is also seen in CNS lymphoma. If CNS lymphoma is suspected, it is recommended that steroids be postponed until after biopsy, if possible.

**37. D**

Gangliogliomas, pilocytic astrocytomas, and pleomorphic xanthoastrocytomas have prominent eosinophilic granular bodies; subependymomas do not.

**38. C**

Subependymal giant cell astrocytomas (SEGAs) are associated with TSC. SEGAs are associated with mutations in *TSC1* and *TSC2*, which are genes that cause TSC. Some SEGAs are treated with mTOR inhibitors, such as everolimus.

Patients with ataxia–telangiectasia are at increased risk for leukemia and lymphoma.

Von Hippel–Lindau disease, which is caused by mutations on chromosome 3, is associated with hemangioblastomas, pheochromocytomas, and renal cell carcinomas. It is caused by mutations in the gene *VHL*, which encodes a protein that inhibits VEGF. Belzutifan (Welireg), which is an inhibitor of hypoxia-inducible factor 2 alpha (HIF-2$\alpha$), has been approved for treatment of adults with von Hippel–Lindau disease with CNS hemangioblastoma, renal cell carcinoma, or a pancreatic neuroendocrine tumor not requiring surgery.

NF type 1 is associated with pilocytic astrocytomas, most commonly in the optic pathway. Optic pathway gliomas in patients with NF type 1 often do not progress and typically can be managed conservatively.[3]

**39. D**

This patient is most likely to have Ma2 (also known as Ta) autoantibodies. (Interestingly, Niemann–Pick type C can also cause cataplexy and vertical gaze palsy.)

CASPR autoantibodies are associated with Morvan syndrome, which may be due to thymoma. Morvan syndrome is associated with peripheral nerve hyperexcitability such as neuromyotonia; neuropsychiatric symptoms such as hallucinations; and dysautonomia. Multiple other autoantibodies are also associated with thymoma.

Dipeptidyl-peptidase-like protein 6 (DPPX) autoantibodies are associated with significant weight loss, encephalitis, diarrhea, and hematologic cancers.[7]

Immunoglobulin-like cell adhesion molecule 5 (IgLON5) autoantibodies can cause symptoms that resemble progressive supranuclear palsy. They are associated with adenocarcinoma.[7]

Autoantibodies to mGlu receptor 5 are associated with Ophelia syndrome (a limbic encephalitis) and Hodgkin lymphoma.[7]

**40. True**

Areas of necrosis can be seen in low-grade ependymomas. Necrosis does not have the same meaning in ependymomas as in astrocytomas. Brisk mitotic activity and microvascular proliferation are characteristics of high-grade ependymomas.[5]

**41. D**

Both pilocytic astrocytoma and hemangioblastoma can appear as cysts with a mural nodule in the cerebellum. In this patient, the histology findings (i.e., Rosenthal fibers, eosinophilic granular bodies, microcysts, and bipolar cell processes) are consistent with pilocytic astrocytoma.

The most common cerebellar masses in children are pilocytic astrocytomas, medulloblastomas, and ependymomas.[4]

**42. True**

Carcinomatous meningitis and lymphomatous meningitis can be associated with very low CSF glucose levels.

**43. C**

Retinoblastoma is a small blue cell tumor associated with Flexner–Wintersteiner (real) rosettes. The gene is on chromosome 13. It is the most common eye malignancy in children. It typically manifests as leukocoria or strabismus.

Patients with hereditary retinoblastoma are at risk for second neoplasms, such as osteosarcoma and melanoma.

The term *trilateral retinoblastoma* is used if a patient has bilateral retinoblastomas and an intracranial tumor in the suprasellar or pineal region, such as a pineoblastoma.

**44. D**

Women diagnosed with anti-NMDA receptor encephalitis should be evaluated for an ovarian teratoma. In addition to seizures and altered mental status/psychosis, patients may have orofacial dyskinesia, autonomic dysfunction, and hypoventilation.[7]

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**45. A**

Anti-Hu/ANNA-1 and anti-CV2 autoantibodies can cause pseudo-obstruction (Ogilvie syndrome).[7]

Anti-Hu/ANNA-1 antibodies are associated with small cell lung cancer (SCLC). If patients have encephalomyelitis and SCLC, anti-Hu/ANNA-1 antibodies should be suspected. Anti-Hu/ANNA-1 antibodies can also cause brainstem encephalitis, limbic encephalitis, cerebellar ataxia, and sensory neuronopathy.

Anti-amphiphysin antibodies, which are associated with breast cancer, can cause stiff-person syndrome and encephalomyelitis. Anti–glutamic acid decarboxylase (anti-GAD) antibodies are also associated with stiff-person syndrome, but they are typically nonparaneoplastic.[7] However, anti-GAD 65 antibodies can be seen with SCLC.

Anti-Ri/ANNA-2 antibodies cause opsoclonus–myoclonus, brainstem encephalitis, and cerebellar degeneration.

Anti-Yo antibodies occur with gynecologic and breast cancers. They cause cerebellar degeneration.

Cerebellar degeneration is also seen with anti-Tr antibodies, which have been found in patients with Hodgkin lymphoma. Anti-Tr antibodies are also called anti-DNER antibodies; DNER is delta/notch-like epidermal growth factor–related receptor.

**46. B**

Antibodies to P/Q-type voltage-gated calcium channels cause Lambert–Eaton myasthenic syndrome.

Anti-AMPA receptor antibodies cause limbic encephalitis.

Antibodies to voltage-gated potassium channels occur in neuromyotonia. They can occur with malignant thymoma.

Antibodies to mGluR1 cause cerebellar degeneration.

Antibodies to LGI1 protein cause limbic encephalitis with faciobrachial dystonic seizures.

**47a. B and 47b. C**

Antoni A and Antoni B patterns and Verocay bodies are seen in schwannomas. Antoni A refers to the densely packed tissue, Antoni B refers to the loosely packed tissue, and Verocay bodies refer to the pattern of nuclear palisades seen in these tumors.

Schwannomas arising from cranial nerve VIII are the most common tumor in the cerebellopontine angle. They stain with S100, whereas meningiomas arising in this region do not.

The second most common tumor in the cerebellopontine angle is meningioma. There are multiple histologic variants of meningiomas. Some common findings are whorls and psammoma bodies. Calcification or cysts may be present.

Ependymomas can occur in the cerebellopontine angle, but they are not as common. Ependymomas are characterized by perivascular pseudorosettes.

Central neurocytomas are low-grade intraventricular tumors. The cells of the tumor can have perinuclear halos, similar to oligodendrogliomas, but they are synaptophysin positive and glial fibrillary acidic protein negative.

Bilateral schwannomas of the vestibular nerve are characteristic of neurofibromatosis type 2/NF2-related schwannomatosis. This condition is also associated with astrocytomas, ependymomas, and meningiomas.

TSC is associated with SEGAs. Enhancement of a subependymal nodule should raise concern for transformation to a SEGA.[8]

NF type 1 is associated with optic nerve gliomas, astrocytomas, schwannomas, meningiomas, neurofibromas, and malignant peripheral nerve sheath tumors. Optic nerve gliomas are the most common tumor in NF type 1. Sphenoid wing dysplasia and areas of myelin vacuolization (formerly referred to as "unidentified bright objects") may also be seen on brain MRI in patients with NF type 1. Selumetinib, which is a mitogen-activated protein kinase kinase (MEK) inhibitor, has been used to treat inoperable plexiform neurofibromas.

**48. D**

Of the medications listed, methotrexate is most likely to cause chronic encephalopathy. It can cause aseptic meningitis and acute, subacute, and chronic encephalopathy. Radiation is a risk factor for methotrexate-induced encephalopathy. Patients may also have a stroke-like syndrome from methotrexate. They may have a hemiparesis that changes from one side to the other.

Cyclosporin, etoposide, ifosfamide, and tamoxifen can cause acute encephalopathy. Methylene blue and thiamine have been used to treat encephalopathy caused by ifosfamide.

**49. A**

Charcot–Marie–Tooth disease is a risk factor for severe neuropathy from vincristine. Patients should be screened for neuropathy before receiving vincristine.

**50. C**

Among the neurological complications of chemotherapy, peripheral neuropathy is common. In some cases, peripheral neuropathy can worsen after discontinuation of chemotherapy (coasting).

Long-term complications of radiation include cognitive decline, secondary brain tumors, vasculopathy, vascular anomalies, strokelike migraine attacks, optic neuropathy, plexopathies, myelopathy, and ototoxicity.[9,10] Secondary brain tumors, such as meningiomas and gliomas, can occur after radiation. In addition, radiation necrosis can resemble brain tumor recurrence; bevacizumab has been used for treatment.[10] Radiation can also cause vasculopathy and vascular abnormalities that can cause stroke. [9,10] Strokelike migraine attacks after radiation therapy (SMART) syndrome can present as focal seizures.[10] Radiation-related plexopathies can be associated with myokymic discharges on EMG, which help differentiate them from tumor-related plexopathies.[10]

BRAF inhibitors can cause paradoxical stimulation of tumor growth in pediatric low-grade astrocytoma with the *KIAA1549-BRAF* truncation/fusion alteration.[4]

**51. B**

Bevacizumab is an antibody that targets VEGF. It has been used in patients with recurrent malignant glioma and in patients with radiation necrosis.[10] It is a "steroid-sparing agent" and can help restore the blood–brain barrier.[11] Stroke is a potential side effect. Bevacizumab has also been associated with cerebral hemorrhage and posterior reversible encephalopathy syndrome (PRES).[9] (Examples of other chemotherapies that are associated with PRES include methotrexate, cisplatin, and vincristine.[12] Cisplatin can also cause peripheral neuropathy and ototoxicity.)

Anakinra is an interleukin-1 receptor antagonist.

Ibrutinib is a Bruton tyrosine kinase inhibitor that can be used to treat refractory lymphoma. It can be associated with opportunistic fungal infections such as *Aspergillus*.[13]

Ipilimumab was the first approved immune checkpoint inhibitor. It binds to cytotoxic T lymphocyte antigen-4 (CTLA-4).[14] It can cause hypophysitis.[11]

Tocilizumab is an interleukin-6 receptor antagonist that has been used to treat cytokine release syndrome, which can occur with chimeric antigen receptor (CAR) T-cell therapy.[14] It is not as helpful for immune effector cell-associated neurotoxicity syndrome (ICANS), which is another potential complication of CAR T-cell therapy. ICANS is better treated with dexamethasone.[14]

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# 18.

# NEURO-OPHTHALMOLOGY

## QUESTIONS

1. **What is the term for the region of the retina with the greatest visual acuity?**
   A. Fovea
   B. Macula
   C. Optic disc

2. **Which of the following is the best description of an image on the retina compared to the actual object?**
   A. The image on the retina is inverted compared to the object.
   B. The image on the retina is reversed compared to the object.
   C. The image on the retina is reversed and inverted compared to the object.

3. **When comparing rods and cones, which of the following statements are true for rods, and which are true for cones?**
   1) More numerous
   2) More prevalent at the region of greatest visual acuity
   3) Detect colors
   4) Poor spatial and temporal resolution
   5) More useful in dim lighting
   A. True for rods
   B. True for cones

4. **In the retina, which cells receive impulses directly from the photoreceptors?**
   A. Amacrine cells
   B. Bipolar cells
   C. Ganglion cells
   D. Horizontal cells

5. **The optic nerve is formed from the axons of which type of cells?**
   A. Amacrine cells
   B. Bipolar cells
   C. Ganglion cells
   D. Horizontal cells

6. **Where do most fibers of the optic tract synapse?**
   A. Lateral geniculate body of the thalamus
   B. Midbrain
   C. Optic chiasm

7. **A 70-year-old presents with double vision, weight loss, new headaches, and scalp tenderness. On exam, the temporal artery is pulseless. Which of the following should be done first?**
   A. Initiate steroids.
   B. Refer to ophthalmology.
   C. Refer to the stroke clinic.
   D. Consult neurosurgery for revascularization.

8. **True or false?**
   The pupillary light reflex does *not* involve the cortex.

9. **Which of the following muscles does *not* affect eyelid position?**
   A. Levator palpebrae superioris
   B. Superior tarsal muscle (Müller's muscle)
   C. Orbicularis oculi
   D. All of the above affect eyelid position.

10. **Which of the following muscles is *not* innervated by the oculomotor nerve?**
    A. Ciliary muscle
    B. Iris sphincter
    C. Müller's muscle
    D. Superior rectus

11. **True or false?**
    A nuclear third nerve palsy can cause bilateral ptosis and bilateral gaze abnormalities.

12. **A 50-year-old woman has double vision when using the right eye but not the left. A pinhole occluder resolves the symptom. What is the most likely etiology?**
    A. A lesion of the medial longitudinal fasciculus (MLF)
    B. Charles Bonnet syndrome
    C. Ocular cause
    D. Optic chiasm lesion
    E. Thalamic lesion

13. **A lesion in which area can cause alternating anisocoria (i.e., the ipsilateral pupil is larger in the light but smaller in the dark)?**
    A. Cavernous sinus
    B. Hypothalamus
    C. Orbit
    D. Brainstem

14. **A lesion in which area can cause bilateral fourth nerve palsies?**
    A. Anterior medullary vellum
    B. Cavernous sinus
    C. Meckel's cave
    D. Orbit

15. **True or false?**
    Injury to the right trochlear nucleus causes a right fourth nerve palsy but can also cause an ipsilateral Horner syndrome if the adjacent sympathetic fibers are involved.

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**16. If a patient has an abducens palsy and an ipsilateral postganglionic Horner syndrome, where is the lesion most likely to be?**

A. Anterior medullary vellum
B. Cavernous sinus
C. Meckel's cave
D. Orbit

**17. What is the difference between orbital apex syndrome and cavernous sinus syndrome?**

A. Cranial nerve IV (CN 4) is involved in the cavernous sinus syndrome but not in the orbital apex syndrome.
B. CN 5 (V1) is involved in the cavernous sinus syndrome but not in the orbital apex syndrome.
C. CN 5 (V2) is spared in orbital apex syndrome, but the optic nerve may be involved.
D. CN 6 is involved in the cavernous sinus syndrome but not in the orbital apex syndrome.

**18. Fill in the blank: The frontal eye field is located in the posterior part of the middle frontal gyrus, which is known as Brodmann area ___________.**

A. 7
B. 8
C. 17
D. 18

**19. Fill in the blank: The frontal eye fields regulate ______________________.**

A. Saccadic eye movements
B. Smooth pursuit
C. Vertical eye movements

**20. Which of the following conditions is *least* likely to affect the eye?**

A. Neurofibromatosis type 1
B. Tuberous sclerosis complex
C. Sturge–Weber syndrome
D. Von Hippel–Lindau disease
E. Rett syndrome

**21. A female patient with a history of epileptic spasms is found to have chorioretinal lacunae. Which of the following findings is likely to be present on magnetic resonance imaging (MRI)?**

A. Agenesis of the corpus callosum
B. Double cortex
C. Lissencephaly
D. Periventricular nodular heterotopia

**22. Which of the following visual defects is caused by a lesion of the left temporal optic radiations?**

A. Right superior quadrantanopia
B. Right inferior quadrantanopia
C. Right homonymous hemianopia with macular sparing
D. Left inferior quadrantanopia
E. Right homonymous sectoranopia

**23. A 40-year-old woman with diabetes, hypercholesterolemia, and coronary artery disease presents with double vision that improves when she covers one of her eyes. She has no headache, vomiting, weight loss, or pain. On examination, she cannot abduct the right eye. Inflammatory markers are normal. What is the most likely diagnosis?**

A. Temporal arteritis
B. Ischemic right abducens palsy
C. Cavernous sinus thrombosis
D. Myasthenia gravis

**24. A 19-year-old woman presents with decreased vision. The symptoms started a few days earlier. She has a left afferent pupil defect, red desaturation and a central scotoma in the left eye, and pain with left eye movement. The funduscopic examination is normal. What is the most likely diagnosis?**

A. Optic neuritis
B. Idiopathic intracranial hypertension
C. Multiple sclerosis
D. Tonic pupil

**25. A 50-year-old man presents with decreased vision in the left eye. On examination, he also has decreased color vision in the left eye. He has optic nerve edema on the right. He also has decreased olfaction. What is the most likely diagnosis?**

A. Anterior ischemic optic neuropathy
B. Leber hereditary optic neuropathy
C. Olfactory groove meningioma
D. Optic neuritis

**26. A 55-year-old man with hypertension and diabetes presents with sudden, painless vision loss. He does not have a headache or systemic symptoms. He has an altitudinal visual field defect and a relative afferent defect. On funduscopic examination, the optic disc is swollen and there are flame-shaped hemorrhages. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level are normal. What is the most likely diagnosis?**

A. Arteritic anterior ischemic optic neuropathy (AAION)
B. Nonarteritic anterior ischemic optic neuropathy
C. Posterior ischemic optic neuropathy
D. Tolosa–Hunt syndrome

**27. What is the most common cause of optic nerve infarct (anterior ischemic optic neuropathy)?**

A. Carotid occlusive disease
B. Temporal arteritis
C. Idiopathic
D. Tolosa–Hunt syndrome

**28. Match the visual field defect with the location of the lesion. (One option will not be used.)**

1) Monocular vision loss
2) Bitemporal hemianopia
3) Contralateral inferior quadrantanopia

A. Optic nerve
B. Optic chiasm

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C. Parietal lobe
D. Temporal lobe

**29. What is the most likely cause of binasal hemianopia?**
A. A lesion that compresses the chiasm
B. Calcified internal carotid arteries
C. Transection of the optic nerve at the chiasm

**30. A 24-year-old postpartum woman presents with severe headache and impaired vision. There is a central scotoma in the right eye, and there is a superior temporal quadrantanopia in the left eye. What is the most likely diagnosis?**
A. Sinus venous thrombosis
B. Pituitary apoplexy
C. Brainstem stroke
D. Stroke in the posterior cerebral artery distribution

**31. A patient is nonresponsive and has pinpoint pupils in midposition that do not move with the doll's eye maneuver. Where is the lesion?**
A. Thalamus
B. Midbrain
C. Pons
D. Medulla

**32. Which of the following statements is *false*?**
A. Visual loss from cataracts typically causes a relative afferent pupillary defect (RAPD).
B. Lesions of the optic tract can cause an RAPD.
C. Excluding trauma, the presence of anisocoria and an RAPD usually indicates that two disease processes are occurring.
D. Significant retinal disease can cause an RAPD.
E. Pretectal lesions can cause a contralateral RAPD without visual field loss.

**33. A 27-year-old woman is involved in a motor vehicle crash. She reports eye and neck pain. On examination, she has unilateral ptosis and miosis. What is the most likely diagnosis?**
A. Cavernous sinus thrombosis
B. Carotid dissection
C. Frontal lobe contusion
D. Hypothalamic hematoma

**34. Which of the following structures is *not* involved in causing the pupil to constrict with light in the pupillary light reflex?**
A. Ganglion cells of the retina
B. Pretectal nucleus
C. Edinger–Westphal nucleus
D. Ciliospinal center
E. Ciliary ganglion

**35. A 20-year-old woman presents with double vision. When she looks to the left, neither eye moves. She is not able to adduct the right eye but is able to abduct it. She cannot adduct the left eye. What is her diagnosis?**
A. Internuclear ophthalmoplegia (INO)
B. One-and-a-half syndrome
C. Left cranial nerve VI palsy
D. Right cranial nerve III palsy

**36. True or false?**
The vestibulo-ocular reflex is preserved with supranuclear lesions.

**37. A 40-year-old woman presents with double vision. On examination, she has ptosis on the right, her right eye is deviated downward and outward, and her right pupil is dilated. Which diagnosis is most likely?**
A. Cavernous sinus thrombosis
B. Increased intracranial pressure
C. Posterior communicating artery aneurysm
D. Vasculopathy

**38. A woman presents with impaired upgaze, impaired convergence, and abnormal pupillary responses. Where is the lesion?**
A. Midbrain
B. Pons
C. Medulla
D. Flocculonodular lobe of the cerebellum

**39. A patient has unusual eye movements. His eyes beat to one side, slow, stop, and then beat to the other side. This repeats every 2 minutes. Where is the lesion?**
A. Midbrain
B. Pons
C. Medulla
D. Flocculonodular lobe of the cerebellum

**40. A 16-year-old patient complains of headaches at the back of his head. He has downbeat nystagmus. Which diagnosis is most likely?**
A. Multiple sclerosis
B. Arnold–Chiari malformation
C. Retinoblastoma
D. Pituitary tumor

**41. Sudden blindness may result from occlusion of which branch of the ophthalmic artery?**
A. Central retinal artery
B. Supraorbital artery
C. Frontal artery
D. Lacrimal artery

**42. A patient in the intensive care unit has a dilated pupil. Pharmacologic dilation is suspected. Which medication is most likely to determine if this is correct?**
A. Apraclonidine 0.5% eye drops
B. Cocaine 4% eye drops
C. Hydroxyamphetamine 1% eye drops
D. Pilocarpine 2% eye drops

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43. **Which of the following is more likely to be found in a patient with pseudopapilledema than a patient with papilledema?**

A. Hemorrhages
B. Leakage on fluorescein angiogram
C. Spontaneous venous pulsations
D. Transient visual obscurations
E. Visual field defects

44. **Fill in the blank: The primary visual cortex is known as Brodmann area ______________.**

A. 7
B. 8
C. 17
D. 18

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# NEURO-OPHTHALMOLOGY

## ANSWERS

**1. A**

The fovea is the area of the retina with the greatest visual acuity. Cones are closely packed in the fovea, and color discrimination is most precise here. No ganglion cells are present in the fovea.

The macula also has high visual acuity. It surrounds the fovea.

The optic disc is where the axons from the ganglion cells leave the retina to become the optic nerve. There are no photoreceptors over this area. The lack of photoreceptors over the optic disc creates a blind spot.

**2. C**

The image on the retina is reversed and inverted compared to the object.

**3.**

1) A
2) B
3) B
4) A
5) A

Rods have poor spatial and temporal resolution but are more numerous and more useful in dim lighting. Rods contain rhodopsin.

Cones are more prevalent at the region of greatest visual acuity (the fovea) and detect color.

Rods and cones in the retina are involved in the pupillary light response. They mediate rapid changes in pupil size with alterations in lighting.

A small fraction of retinal ganglion cells contain melanopsin, are photosensitive, and are involved in the pupillary response to light. These cells project to the suprachiasmatic nucleus and regulate circadian rhythm.[1]

**4. B**

Bipolar cells receive impulses directly from the photoreceptors.

Visual information entering the eye first reaches the layer containing rods and cones, which are photoreceptor cells. Pigments in these photoreceptor cells transform energy from light into electrical signals, which are transmitted to the bipolar cells. This information is then carried to ganglion cells.

Photoreceptors and bipolar cells are unusual compared to other neurons because they do not use action potentials. Neurotransmitters are released in a graded manner that depends on the membrane potential.

**5. C**

The optic nerve is formed from the axons of ganglion cells.

Amacrine cells and horizontal cells are interneurons that increase visual contrast through their interactions with other cells.

**6. A**

Most fibers of the optic tract synapse in the lateral geniculate body. Layers 2, 3, and 5 of the lateral geniculate body receive uncrossed fibers; layers 1, 4, and 6 receive crossed fibers.

Fibers from the optic tract also travel to the superior colliculus and the pretectal nuclei in the midbrain. The superior colliculus is involved with saccades, and the pretectal nuclei are involved in pupillary responses. Information travels from the superior colliculus and pretectal nuclei to the pulvinar and then to the temporoparieto-occipital association cortex.

Fibers from the optic tract also travel to the suprachiasmatic nucleus, which regulates circadian rhythms.

**7. A**

This patient has giant cell arteritis (GCA), which can cause arteritic anterior ischemic optic neuropathy (AAION). Steroids should be initiated to prevent vision loss.

GCA can present with vision loss and/or diplopia. The incidence increases with age. In the 2022 American College of Rheumatology diagnostic criteria, an age of at least 50 years is an absolute requirement.[2]

GCA can cause fever, headache, jaw claudication, scalp tenderness, malaise, anorexia, weight loss, and polymyalgia rheumatica. The temporal artery may be pulseless. Laboratory studies show elevated inflammatory markers such as CRP and ESR. The patient may have thrombocytosis or anemia. Temporal artery biopsy is diagnostic of GCA. Treatment is with steroids. Prompt recognition and treatment are required to prevent permanent vision loss. If GCA is suspected, steroids should be initiated before a temporal artery biopsy is obtained. Tocilizumab, an interleukin-6 inhibitor, has been used as adjunctive treatment for GCA.[3]

**8. True**

Patients with cortical blindness have preserved pupil light reflexes. They can also have normal visual evoked potentials (see Figure 18.1).

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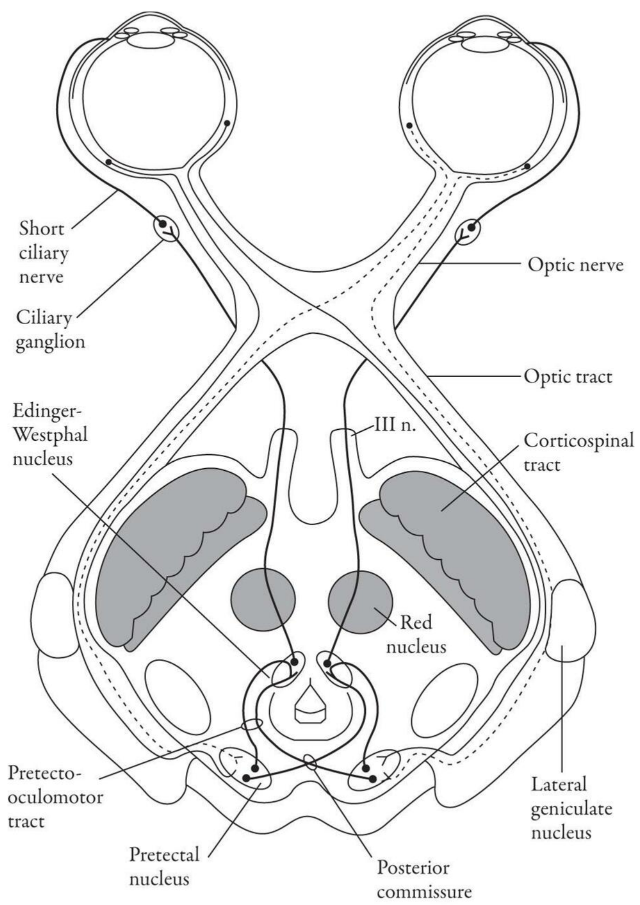

**Figure 18.1** Light reflex pathway. SOURCE: From Sundaram V, Barsam A, Alwitry A, Khaw P. *Training in Ophthalmology*, Fig. 9.1. New York: Oxford University Press; 2009.

Patients with cortical blindness—for instance, from bilateral posterior cerebral artery strokes—may deny their blindness. The term for this is Anton syndrome.

**9. D**

The levator palpebrae superioris elevates the upper eyelid. It is innervated by CN 3.

The superior tarsal muscle is also responsible for elevating the eyelid. It is innervated by sympathetic nerves.

The orbicularis oculi muscle is responsible for eyelid closure and is innervated by CN 7.

**10. C**

Müller's muscle is innervated by sympathetic nerves.

The superior rectus, iris sphincter, and ciliary muscle are innervated by CN 3.

**11. True**

Due to the central caudal nucleus, a nuclear third nerve palsy can cause bilateral ptosis. The central caudal nucleus is one of the subnuclei of the oculomotor nucleus. It innervates both levator palpebrae superior muscles.

A nuclear third nerve palsy can also cause bilateral superior rectus weakness.

The superior rectus is innervated by the contralateral CN 3 nucleus. Fibers from one superior rectus nucleus decussate and cross through the contralateral superior rectus nucleus before proceeding to the muscle.

**12. C**

Ocular abnormalities can cause monocular diplopia. A pinhole occluder can aid in the diagnosis.[4]

A patient with impaired vision who has visual hallucinations has Charles Bonnet syndrome.

**13. A**

A cavernous sinus lesion can cause both a Horner syndrome and CN 3 palsy, which can result in alternating anisocoria.

Horner syndrome typically causes anisocoria that is worse in the dark. Anisocoria is worse in the light with third nerve palsies and with tonic pupils.

**14. A**

A lesion in the anterior medullary vellum, where the trochlear nerves decussate, can cause bilateral CN 4 palsies. For example, head trauma can cause injury to the anterior medullary vellum. Patients with bilateral trochlear nerve palsies have a characteristic "chin down" position.

**15. False**

Injury to the right trochlear nucleus causes a *left* fourth nerve palsy because the nerve decussates. There may also be a Horner syndrome on the right if the adjacent sympathetic fibers are involved in the lesion.

Horner syndrome with a contralateral fourth nerve palsy suggests a lesion of the fourth nerve nucleus or its fascicle prior to decussation in the anterior medullary vellum.

**16. B**

A lesion in the cavernous sinus can cause an abducens palsy with an ipsilateral postganglionic Horner syndrome.

The anterior medullary vellum is where the trochlear nerves decussate.

The trigeminal ganglion is located in Meckel's cave.

**17. C**

The orbital apex syndrome, cavernous sinus syndrome, and superior orbital fissure syndrome can all involve CN 3, CN 4, the V1 division of CN 5, and CN 6. Involvement of CN 2 helps differentiate the orbital apex syndrome from the superior orbital fissure syndrome: CN 2 is involved in the former but spared in the latter. Involvement of the V2 division of CN 5 suggests cavernous sinus syndrome. Cavernous sinus syndrome may also involve the carotid artery and oculosympathetic fibers. Division V3 can be involved if there is spread to Meckel's cave.

**18. B**

The frontal eye fields are in the middle frontal gyrus in Brodmann area 8.

**19. A**

Voluntary saccades are controlled by the contralateral frontal lobe. There are projections from the frontal lobe to the superior colliculus and to the brainstem saccade centers. There is also a parietocollicular pathway that produces reflexive saccades.

Burst neurons in the paramedian pontine reticular formation (PPRF) initiate horizontal saccades. The nucleus prepositus hypoglossi and the medial vestibular nucleus act as horizontal gaze neural integrators.

The rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) and interstitial nucleus of Cajal are responsible for vertical saccades.

Smooth pursuit requires an intact ipsilateral occipital lobe.

**20. E**

Rett syndrome is least likely to involve the eye.

Ataxia–telangiectasia is associated with bilateral bulbar conjunctival telangiectasias but also with abnormal eye movements. Initially, patients have ocular motor apraxia. Then, smooth pursuit is impaired. Later, patients develop complete supranuclear ophthalmoplegia.

Klippel–Trenaunay–Weber syndrome, which is a disorder of soft tissue and bony hypertrophy and cutaneous vascular abnormalities, is associated with multiple eye findings: orbital varix, heterochromia iridis, varicosities of the retina, and choroidal angioma.

Neurofibromatosis type 1 is associated with Lisch nodules. Also, patients can have an optic pathway glioma.

Sturge–Weber syndrome is associated with glaucoma, typically ipsilateral to the facial angioma. Patients can also have choroidal hemangiomas, heterochromia iridis, and angiomas of the conjunctiva and sclera.

Tuberous sclerosis complex is associated with retinal astrocytic hamartomas.

Von Hippel–Lindau disease is associated with retinal hemangioblastomas, which are also known as retinal angiomas.

Wyburn–Mason syndrome, also known as retinocephalic vascular malformation, is associated with ocular arteriovenous malformations (AVMs) such as AVM of the retina, in the orbit, or involving the optic nerve, as well as intracranial AVM.

**21. A**

This is Aicardi syndrome, which is X-linked dominant. Patients with Aicardi syndrome have the triad of epileptic spasms, agenesis of the corpus callosum, and chorioretinal lacunae.

**22. A**

A lesion of the left temporal optic radiations causes a right superior quadrantanopia.

A lesion of the left parietal optic radiations causes a right inferior quadrantanopia.

A right homonymous hemianopia with macular sparing occurs with left occipital lobe lesions.

A right homonymous sectoranopia occurs with lesions of the left lateral geniculate nucleus.

**23. B**

This patient has an ischemic abducens palsy, which can occur with microvascular disease. The normal inflammatory markers and lack of headache make temporal arteritis less likely. If she were older, temporal arteritis would be higher on the differential. Other cranial nerves would probably be involved if the patient had a cavernous sinus thrombosis.

**24. A**

This is retrobulbar optic neuritis. Optic neuritis can be associated with papillitis, in which case the disc is swollen.

She does not have papilledema, so idiopathic intracranial hypertension is unlikely.

There is not enough information to diagnose the patient as having multiple sclerosis.

A patient with a tonic pupil, or Adie's tonic pupil, has anisocoria that is worse in the light. The pupil reacts slowly to sustained bright light. It reacts with accommodation but then redilates slowly. The fact that the pupil reacts better with accommodation than with light is referred to as light-near dissociation (see Box 18.1). A tonic pupil would *not* have an afferent pupil defect or red desaturation.

**_Box 18.1_ CAUSES OF LIGHT-NEAR DISSOCIATION**

- Adie's tonic pupil
- Argyll Robertson pupil
- Diabetes
- Optic neuropathy
- Parinaud syndrome
- Retinopathy (severe)

A tonic pupil can be accompanied by decreased reflexes. This combination is known as Holmes–Adie syndrome. Ross syndrome is a triad of a tonic (Adie) pupil, decreased reflexes, and segmental anhidrosis.

Causes of light-near dissociation include lesions of the dorsal midbrain, ciliary ganglion, and optic nerves (severe optic neuropathy).[1] The postganglionic parasympathetics travel from the ciliary ganglion through the short ciliary nerves. These nerves innervate the ciliary muscle, which is responsible for accommodation, and the iris sphincter, which is responsible for pupil constriction.

**25. C**

This patient has Foster Kennedy syndrome, which is caused by an olfactory groove meningioma. Patients with Foster Kennedy syndrome have decreased visual acuity, decreased color vision, and optic atrophy in the ipsilateral eye due to compression of the optic nerve by the tumor. There is papilledema in the contralateral eye due to increased intracranial pressure. These patients may have anosmia as well. (Pseudo-Foster Kennedy syndrome refers to a patient *without* a tumor who has optic disc edema on one side and optic disc atrophy on the other side.)

Leber hereditary optic neuropathy is a mitochondrial disorder that usually manifests in childhood or young adulthood. Patients may present with sudden vision loss. A cecocentral scotoma (affecting central vision and extending to the blind spot) is characteristic. Initially, the symptoms are unilateral, but severe bilateral vision loss eventually occurs. Idebenone is a new treatment for Leber hereditary optic neuropathy.[5]

**26. B**

The patient's history and examination findings are consistent with nonarteritic anterior ischemic optic neuropathy (NAION). NAION is a common cause of acute optic neuropathy in patients older than age 50 years. It often presents upon awakening and is usually not painful. Disc edema with flame-shaped hemorrhages can be seen in NAION.

Risk factors include a crowded optic disc, hypertension, diabetes, obstructive sleep apnea, amiodarone, and phosphodiesterase 5 inhibitors such as sildenafil.[3]

AAION, which is associated with GCA, can cause a pale optic disc with edema. This patient does not have a headache, systemic symptoms, or elevated inflammatory markers, so AAION is less likely.

Optic nerve enhancement, a visual field defect affecting central vision, and pain are more likely in optic neuritis than NAION.[3]

The presence of optic disc edema excludes posterior ischemic optic neuropathy, in which ischemia is retrobulbar. Prolonged surgeries are a risk factor for posterior ischemic optic neuropathy.[3]

**27. C**

Most cases of anterior ischemic optic neuropathy are idiopathic.

Tolosa–Hunt syndrome is an inflammatory condition that can occur in the cavernous sinus and cause multiple cranial neuropathies. It is associated with painful ophthalmoplegia and is treated with corticosteroids.

**28.**

1) A. Monocular vision loss occurs with optic nerve lesions.
2) B. A lesion at the optic chiasm, such as a pituitary tumor, can cause bitemporal hemianopia.
3) C. A lesion affecting the optic radiations traveling through the parietal lobe causes a contralateral inferior quadrantanopia.

**29. B**

Of the options listed, the most likely cause of binasal hemianopia is calcified internal carotid arteries (see Figure 18.2).

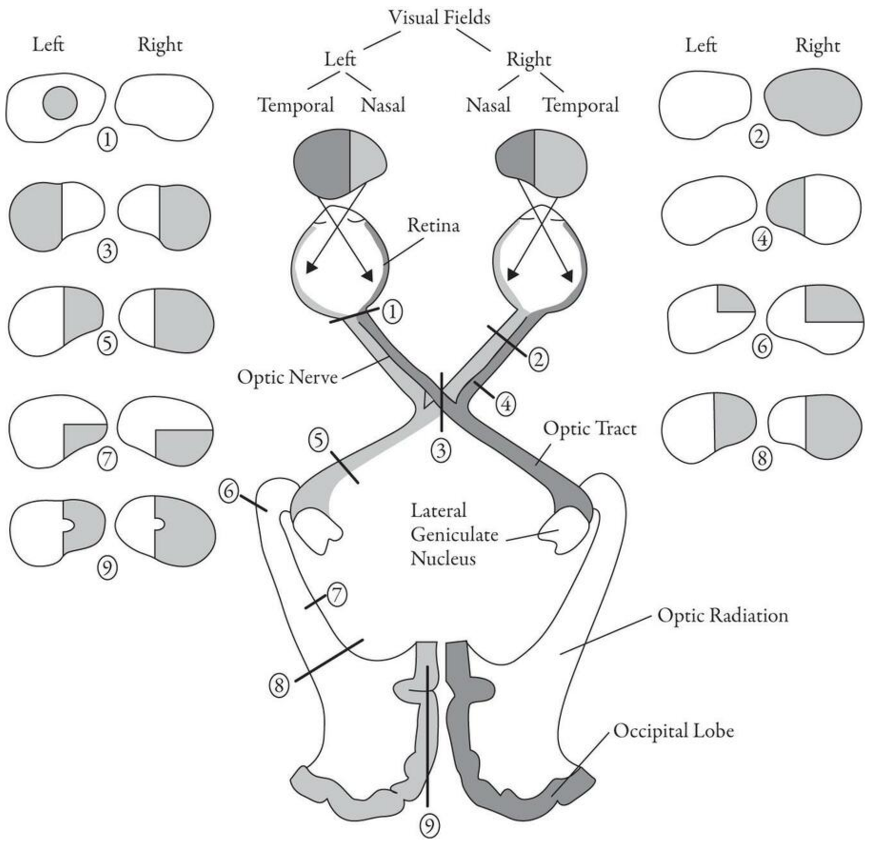

**Figure 18.2** The optic pathway. SOURCE: From Harrison M. *Revision Notes for MCEM Part A*, Fig. A.6.3. New York: Oxford University Press; 2011.

**30. B**

This patient has pituitary apoplexy, which can cause an Addisonian crisis. The visual field defect (junctional scotoma) is consistent with chiasmal compression. Junctional scotoma has been attributed to Wilbrand's knee: At the chiasm, inferonasal fibers decussate and make a forward loop, traveling anteriorly with the contralateral optic nerve before joining the optic tract. (However, this concept is now under scrutiny.)

Chiasmal compression can also cause bitemporal hemianopia.

**31. C**

A lesion in the pons causes pinpoint pupils that are in midposition.

**32. A**

Cataracts do *not* usually cause an RAPD.

RAPD/Marcus–Gunn pupil is tested with the swinging flashlight test: The affected pupil dilates when the light is directed to it, instead of constricting, because less light is perceived (see Box 18.2).

**Box 18.2** CAUSES OF A RELATIVE AFFERENT PUPILLARY DEFECT (RAPD)

- Optic nerve disease
- Significant retinal disease
- Optic tract (when there are more crossed than uncrossed fibers)
- Pretectal lesions (RAPD is contralateral)

**33. B**

Carotid dissection, which can occur after trauma, can manifest as a painful Horner syndrome.

Horner syndrome is due to a lesion in the oculosympathetic pathway, which is a three-neuron pathway. The third-order (postganglionic) fibers travel with the internal carotid artery, so carotid dissection can cause Horner syndrome. Anhidrosis in the lower face is not expected with internal carotid artery dissection because the sympathetic fibers responsible for lower face sweating travel with the external carotid artery rather than the internal carotid artery. However, lesions in the first- and second-order neurons in the oculosympathetic pathway cause anhidrosis in the upper and lower face.

**34. D**

The ciliospinal center, which is located in the intermediolateral cell column at the C8–T2 level of the spinal cord, is part of the oculosympathetic pathway and dilates the pupil. The ciliospinal reflex causes pupillary dilation when the skin of the neck is pinched.

In the oculosympathetic pathway, sympathetic fibers travel from the first-order neuron in the hypothalamus through the brainstem and spinal cord to synapse at the ciliospinal center. Then, second-order (preganglionic) fibers exit the spinal cord and travel through the cervical sympathetic chain, through the brachial plexus, and over the apex of the lung. They synapse in the superior cervical ganglion, which is near the bifurcation of the common carotid artery. The third-order (postganglionic) fibers travel with the internal carotid artery into the cavernous sinus and then to the eye.

**35. B**

This patient has one-and-a-half syndrome.

In the one-and-a-half syndrome, neither eye moves to the side of the lesion (in this case the left side). The only horizontal movement is abduction of the contralateral eye (in this case the right eye). The patient has a conjugate horizontal gaze palsy to the left and an internuclear ophthalmoplegia on right gaze (i.e., impaired adduction of the left eye when looking to the right). Convergence, which is mediated by the medial rectus, is normal. This syndrome is caused by a lesion of the MLF plus the ipsilateral PPRF or the ipsilateral CN 6 nucleus.

A lesion of the MLF alone causes INO. Axons from internuclear neurons in the abducens nucleus in the pons cross the midline and then travel in the MLF to the oculomotor nucleus in the midbrain. With a lesion of the right MLF, the right eye does not adduct with lateral gaze to the left. The left eye abducts and often has nystagmus. Convergence is relatively preserved. Testing saccades can help identify an INO.[4] Bilateral INO can occur in multiple sclerosis.

**36. True**

The vestibulo-ocular reflex is preserved with supranuclear lesions.

**37. C**

This patient has a CN 3 palsy with pupillary involvement, which is most likely caused by a posterior communicating artery aneurysm.

If the pupil were spared, a vasculopathy would be more likely in an older patient.

A cavernous sinus thrombosis would likely cause other cranial nerve palsies as well.

Increased intracranial pressure is more likely to cause an isolated CN 6 palsy than a CN 3 palsy.

**38. A**

This patient has Parinaud syndrome, which is caused by a dorsal midbrain lesion—for example, a pineal tumor. It is characterized by impaired upgaze, impaired convergence, and light-near dissociation of the pupils.

Other midbrain lesions can cause impaired downgaze.

Progressive supranuclear palsy also affects vertical eye movements; downward movements are usually affected more than upward movements.

**39. D**

This patient has periodic alternating nystagmus, which is associated with lesions of the flocculonodular lobe of the cerebellum.

**40. B**

Downbeat nystagmus is seen in patients with lesions at the cervicomedullary junction and can be seen in patients with Arnold–Chiari I malformation.

Wernicke disease is associated with upbeat and downbeat nystagmus.[6]

**41. A**

Sudden blindness may result from occlusion of the central retinal artery.

The ophthalmic artery is a branch of the internal carotid artery. The central retinal artery is a branch of the ophthalmic artery. The central retinal artery has four branches, each of which supplies blood to a quadrant of the retina. Biousse et al. recommended that patients with retinal artery ischemia, such as branch retinal artery occlusion or central retinal artery occlusion, be referred for a stroke evaluation.[7]

Susac syndrome is associated with branch retinal artery occlusion.

**42. D**

Pilocarpine 2% eye drops should correct mydriasis unless the etiology is pharmacologic.[1]

Apraclonidine 0.5% is a weak $\alpha_2$ agonist. It causes a chronic Horner pupil to dilate but not a normal pupil. It should not be used in infants due to a risk for respiratory depression.[1]

Cocaine decreases reuptake of catecholamines from the synaptic cleft. In a patient with Horner syndrome, the normal pupil dilates more than the denervated pupil.[1]

Hydroxyamphetamine drops help differentiate third-order Horner syndrome from first- and second-order Horner syndrome. A patient with a first- or second-order syndrome will have pupil dilation from hydroxyamphetamine, but if there is a third-order syndrome, the pupil will not dilate. (In addition, third-order Horner syndrome is not associated with anhidrosis.)[1]

**43. C**

Spontaneous venous pulsations are more likely to occur in pseudopapilledema.

Obscuration of vessels, hemorrhages, leakage on fluorescein angiogram, transient visual obscurations, and visual defects are more likely to occur in a patient with papilledema.[8]

**44. C**

Information regarding the form, color, and motion of visual stimuli is carried from the lateral geniculate nucleus to the visual cortex through the optic radiations. The primary visual cortex, which is Brodmann area 17, is located in the calcarine fissure of the occipital lobe. Layer 4 of the visual cortex is relatively thick due to the amount of input.

The calcarine cortex consists of the cuneus and the lingual gyrus. The cuneus, which is superior to the lingual gyrus, receives information from the upper quadrants of the retina. The lingual gyrus receives information from the lower retina.

Brodmann areas 18 and 19 are visual association cortex. They are responsible for color perception and object recognition.

Further visual processing is performed in the parieto-occipital association cortex and the occipitotemporal association cortex. Information regarding motion and spatial relationships travels from the primary visual cortex to the parietal lobe in the "where" pathway, also called the dorsal pathway. Information regarding shape and color travels to the temporal lobe from the primary visual cortex in the "what" pathway, also known as the ventral pathway.

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# 19.

# NEURO-OTOLOGY

## QUESTIONS

1. **A 30-year-old man with no known past medical history, who was adopted, presents to the clinic due to progressive hearing loss and dizziness. A computed tomography (CT) scan of head is done, and he is found to have bilateral cerebellopontine angle masses. What is the most likely diagnosis?**
   A. Neurofibromatosis type 1
   B. Neurofibromatosis type 2 (NF2)/NF2-related schwannomatosis
   C. Tuberous sclerosis complex (TSC)
   D. Alport syndrome

2. **A 60-year-old man comes into the hospital with acute loss of hearing associated with gait imbalance and dysmetria. His magnetic resonance imaging (MRI) scan shows an acute stroke. Which artery is most likely to be involved?**
   A. Posterior cerebral artery
   B. Middle cerebral artery
   C. Posterior inferior cerebellar artery
   D. Anterior inferior cerebellar artery (AICA)

3. **A 65-year-old woman presents with dizziness that starts when she sits up in the morning that has been ongoing for a month. The dizziness lasts approximately 20 seconds and subsides when she lays down. The neurologic exam is normal, and the Dix–Hallpike maneuver is positive for right beating nystagmus. What is the best treatment for this patient?**
   A. Meclizine
   B. Prednisone
   C. Benzodiazepine
   D. Vestibular rehabilitation with canalith repositioning

4. **A 49-year-old woman with a history of migraine in her twenties presents to your office due to frequent brief episodes of dizziness. The patient notices the dizziness when she is exercising or in the afternoon after work. The episodes usually last approximately 5–10 minutes. She endorses feeling off balance and nauseated at times, and occasionally she will have a pulsating left-sided headache during the episode. Her MRI brain is negative, and she has a normal audiometry and videonystagmography. What is the most likely diagnosis?**
   A. Persistent postural perceptual dizziness
   B. Vestibular migraine
   C. Benign paroxysmal positional vertigo (BPPV)
   D. Ménière disease

5. **A patient has spontaneous down-beating nystagmus. Where is the lesion most likely to be?**
   A. Cervicomedullary junction
   B. Mamillary bodies
   C. Medial dorsal medulla
   D. Pontine cerebellar junction

6. **Which structure is most closely involved with gaze-evoked nystagmus?**
   A. Cervicomedullary junction
   B. Interstitial nucleus of Cajal
   C. Cerebellar vermis
   D. Flocculonodular lobe

7. **A 70-year-old man presents to the clinic due to 4 weeks of dizziness and visual disturbance. He states that when the symptoms started, he felt a popping sensation near his right ear. Since then, he has had intermittent episodes of feeling like he is floating and seeing the room around him move. Loud sounds can trigger these episodes. What is the most likely diagnosis?**
   A. BPPV
   B. Vestibular migraine
   C. Vestibular neuritis
   D. Superior canal dehiscence

8. **Which structure carries auditory information from the superior olivary complex to the inferior colliculus?**
   A. Cochlear nuclei
   B. Lateral lemniscus
   C. Medial lemniscus
   D. Medial geniculate nucleus

9. **Which of the following structures is important in sound localization in the horizontal plane?**
   A. Inferior olivary nucleus
   B. Semicircular canals
   C. Superior olivary nucleus
   D. Utricle and saccule
   E. Stapedius nerve

10. **Which structure transfers information between the left and right auditory cortices?**
    A. Anterior commissure
    B. Posterior commissure
    C. Corpus callosum
    D. Hippocampal commissure

11. **True or false?**
    A unilateral lesion at the mid pons or higher does *not* cause deafness.

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12. **A 40-year-old man presents with recurrent episodes of vertigo. The episodes last 30 minutes and are associated with tinnitus and a feeling of fullness in his right ear. He has fallen abruptly after a feeling of being pushed to the ground. His neurologic examination is normal between episodes except for decreased hearing in the right ear. His brain MRI is normal. Which procedure needs to be performed?**
    - A. Audiometry
    - B. Electroencephalography
    - C. Epley maneuver
    - D. Sinus CT

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# NEURO-OTOLOGY

## ANSWERS

**1. B**

This patient has neurofibromatosis type 2/NF2-related schwannomatosis with bilateral vestibular schwannomas. (In 2022, there was an international consensus recommendation to rename neurofibromatosis type 2 as NF2-related schwannomatosis.[1]) This is an autosomal dominant condition that affects the *NF2* gene on chromosome 22, which encodes merlin (also known as schwannomin). It is characterized by acoustic neuromas or bilateral schwannomas resulting in progressive hearing loss. Patients can also have meningiomas, intramedullary ependymomas, and schwannomas of the spinal nerves. Cutaneous neurofibromas are not common in NF type 2/NF2-related schwannomatosis.

NF type 1 is also an autosomal dominant condition. It affects the neurofibromin gene on chromosome 17. Patients with NF type 1 have many cutaneous findings, such as café-au-lait spots, neurofibromas, and axillary and inguinal freckling. Plexiform neurofibromas are also one of the diagnostic criteria. Patients with NF1 may also have Lisch nodules of the iris or choroidal anomalies. They can develop optic nerve gliomas. Osseous lesions are also seen in NF1.[2]

TSC is another neurocutaneous disorder that is associated with a risk for tumors. It is *not* common to have bilateral acoustic neuromas in this condition. Patients with TSC are at risk for several types of tumors, including subependymal giant cell astrocytoma, cardiac rhabdomyoma, angiomyolipoma, renal cell carcinoma, and retinal hamartoma. Other central nervous system findings in TSC include subependymal nodules and cortical tubers. Patients with TSC are also at risk for epilepsy, including epileptic spasms, and TSC-associated neuropsychiatric disorder including intellectual delay.[3]

Alport syndrome is an X-linked inherited disorder that results in kidney disease, hearing loss, and vision loss. Bilateral acoustic neuromas are *not* typical of this condition.

**2. D**

Lesions of the AICA, which branches off the basilar artery, can result in acute hearing loss. One of the distal branches of the AICA is the labyrinthine artery, which supplies the inner ear. If there is acute unilateral hearing loss, then brainstem imaging would be imperative to determine if a stroke has affected the AICA or its branches. Other structures involved in AICA strokes include the brachium pontis, the spinothalamic tract, the descending sympathetic tract, cranial nerve VII, the descending tract of cranial nerve V, and the cochlear nucleus. Symptoms that can be seen in an AICA stroke include an ipsilateral Horner syndrome, facial weakness, hemiataxia, dizziness, vertigo, nausea, and tinnitus.[4]

**3. D**

This is an example of BPPV. In the classic case of BPPV, a patient has a sensation of vertigo: dizziness, spinning, and occasionally lightheadedness. This can be accompanied by nausea or vomiting. The diagnosis of BPPV requires diagnostic positional maneuvers that lead to the observation of a canal-specific positional nystagmus. This can be achieved by doing the Dix–Hallpike maneuver. The clinical features that are necessary to make this diagnosis include evaluating the latency, direction, and duration of positional nystagmus.[5] A negative Dix–Hallpike maneuver does not rule out BPPV.

BPPV is the most frequent cause of episodic vertigo in adults. The etiology of BPPV is thought to be due to the presence of otoconia, which are formed by calcium carbonate debris in the semicircular canals, most often the posterior canal. The reasons for otoconia displacement include head trauma, infection, ischemia of the inner ear (labyrinthine artery), rapid head movements, or extension of the head past the horizontal plane. The treatment of BPPV is repositioning the otoconia through maneuvers such as the Epley maneuver, which is often done during vestibular rehabilitation.

Meclizine is an antihistamine medication which is used to treat symptoms such as dizziness, nausea, and vomiting that are associated with motion sickness. Some people use this medication in BPPV to help with their symptoms, but it does not treat the misaligned otoconia that causes BPPV. Similar to meclizine, benzodiazepines and prednisone have been used to help with symptom management.[6]

**4. B**

This patient is experiencing vestibular migraine. The diagnostic criteria of vestibular migraine include a history of migraine and at least five episodes of moderate to severe vestibular symptoms that last between 5 minutes and 72 hours. At least half of these episodes will include one migrainous feature, such as a visual aura, photophobia and phonophobia, or a headache that is unilateral in location, has a pulsating quality, is moderate/severe in intensity, or is aggravated by activity. There is also a temporal association between the patient's vestibular symptoms and migraines.[7]

**5. A**

Spontaneous down-beating nystagmus can be localized to the cervicomedullary junction and cerebellar vermis. Causes include cerebellar ataxias, Chiari malformation, or multiple sclerosis.

A lesion of the mamillary bodies can cause impaired memory and anterograde amnesia.

Injury to the medial medulla can cause spontaneous up-beating nystagmus.

Injury to the pontine cerebellar junction can lead to symptoms such as vertigo, hearing loss, and tremor.[6]

**6. D**

The flocculonodular lobe is involved in gaze-evoked nystagmus. This type of nystagmus can occur when the mechanism that allows a person to hold a gaze is impaired. The flocculonodular lobe of the cerebellum, the nucleus prepositus hypoglossi, and the medial vestibular nucleus give input to the neural integrator that allows for horizontal gaze holding.

The interstitial nucleus of Cajal is involved in vertical and torsional gaze holding.

Injury to the cerebellar vermis can lead to spontaneous down-beating nystagmus.[6,8]

**7. D**

This patient is experiencing superior canal dehiscence. In this condition patients will often feel a sensation of spinning, tilting, oscillopsia, floating, and ear fullness all which can last seconds to minutes. At the onset of symptoms, the patient might experience a popping sensation. Sounds can trigger the above listed sensations. Some symptoms that are associated with superior canal dehiscence include reduced hearing, tinnitus, and nystagmus that is triggered by sounds and autophony.[6,8]

**8. B**

Information from the cochlear nuclei travels to either the ipsilateral or the contralateral superior olive. The crossing fibers are found in the trapezoid body in the pons.

The lateral lemniscus carries auditory information from the superior olivary complex to the inferior colliculus.

The Brainstem auditory evoked potential pathway (BAEP) consists of seven peaks: cranial nerve 8 (Wave I) → cochlear nuclei in the medulla (Wave II) → superior olivary complex in the pons (Wave III) → lateral lemniscus in the pons (Wave IV) → inferior colliculus in the midbrain (Wave V) → medial geniculate nucleus in the thalamus (Wave VI) → auditory radiations (Wave VII).

The BAEP pathway can be remembered by the mnemonic NCSLIMA (see Box 19.1).

### *Box 19.1* PEAKS OF THE BRAINSTEM AUDITORY EVOKED POTENTIAL: NCSLIMA

- **N**erve (cochlear)
- **C**ochlear nuclei
- **S**uperior olive
- **L**ateral lemniscus
- **I**nferior colliculus
- **M**edial geniculate
- **A**uditory cortex

**9. C**

The superior olivary nucleus is involved in sound localization in the horizontal plane.

The semicircular canals, utricle, and saccule are part of the vestibular system. The semicircular canals detect angular acceleration. The utricle and saccule are involved in detection of linear acceleration.

The stapedius nerve, which is innervated by the facial nerve, dampens sound.

**10. C**

The corpus callosum transfers information between the left and right auditory cortices.

**11. True**

A unilateral lesion at the mid pons or higher does not cause hearing loss. Bilateral injury to primary auditory cortex can cause a variety of symptoms depending on the lesions. For instance, bilateral injury can cause cortical deafness, pure word deafness, or auditory agnosia. Even with cortical deafness, the audiogram may be normal.

**12. A**

This patient has Ménière disease. Audiometry should be performed.

Patients with Ménière disease have episodes of vertigo lasting for at least 20 minutes. They can fall abruptly as if pushed to the ground. In addition, patients with Ménière disease have tinnitus or a sensation of fullness in the ear, and low-frequency hearing loss occurs. (With aging, high-frequency hearing loss usually occurs.) Ménière disease is associated with endolymphatic hydrops. Electrocochleography can help confirm the diagnosis; there is a characteristic pattern with hydrops. Salt restriction is recommended for patients with Ménière disease.

There is an association between Ménière disease and migraine. Vestibular migraine may be difficult to differentiate from early Ménière disease, and some patients have both. Significant hearing loss does not occur in vestibular migraine. Vestibular migraine is a common cause of recurrent spontaneous vertigo. The patient with vestibular migraine has both vestibular symptoms and headaches with migrainous features.

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# 20.

# NEUROPATHOLOGY

## QUESTIONS

**1. In a normal brain, it is most common to find neurons in the white matter in which area?**

A. Frontal lobe
B. Parietal lobe
C. Temporal lobe
D. Occipital lobe

**2. Normal ependymal cells stain strongly with which of the following?**

A. Congo red
B. Desmin
C. Vimentin
D. Luxol fast blue

**3. Which of the following statements is *false*?**

A. Astrocytes are unable to proliferate.
B. Astrocytes, oligodendrocytes, and ependymal cells are of ectodermal origin.
C. Astrocytes have intermediate filaments that contain glial fibrillary acidic protein (GFAP).
D. Astrocytes can be found in the white matter.

**4. Which of the following cells are *least* likely to be found in the central nervous system?**

A. Astrocytes
B. Ependymal cells
C. Oligodendrocytes
D. Schwann cells
E. Microglia

**5. Which of the following is most likely to stain blue/purple with hematoxylin and eosin (H&E) stain?**

A. Cytoplasm
B. Nucleus
C. Collagen
D. Myelin

**6. Which of the following cells are most susceptible to hypoxic–ischemic injury?**

A. Astrocytes
B. Hippocampal pyramidal cells of Sommer's sector (CA1)
C. Neurons of cortical layers III, V, and VI
D. Oligodendrocytes

**7. Which of the following features is characteristic of apoptosis?**

A. Activation of intracellular proteases
B. Rupture of the cell membrane
C. Inflammation
D. Random DNA degradation

**8. Which type of astrocytes can be found in hyperammonemia but are especially associated with Wilson disease?**

A. Alzheimer type I astrocytes
B. Alzheimer type II astrocytes
C. Bergmann glia
D. Creutzfeldt astrocytes

**9. Which type of astrocytes are associated with demyelination?**

A. Alzheimer type I astrocytes
B. Alzheimer type II astrocytes
C. Bergmann glia
D. Creutzfeldt astrocytes

**10. What is tau?**

A. A microfilament
B. An intermediate filament
C. An aggregate of tubulin
D. A microtubule-associated protein

**11. Which of the following is the major component of neurofibrillary tangles?**

A. Hyperphosphorylated tau protein
B. Neurofilament protein
C. Ubiquitin
D. Amyloid

**12. Which of the following is *not* characteristic of Alzheimer disease?**

A. Neurofibrillary tangles
B. Senile plaques
C. Granulovacuolar degeneration
D. Hirano bodies
E. Lewy bodies

**13. Which of the following is *not* a tauopathy?**

A. Multiple system atrophy (MSA)
B. Progressive supranuclear palsy (PSP)
C. Corticobasal degeneration (CBD)
D. Chronic traumatic encephalopathy (CTE)

**14. The severity of Alzheimer dementia is *least* likely to correlate with which of the following?**

A. Quantity of diffuse plaques
B. Distribution of neurofibrillary tangles
C. Quantity of neuritic plaques
D. Location of β-amyloid plaques

15. **A low Braak stage indicates that neurofibrillary tangles are limited to which of the following areas?**
    A. Transentorhinal cortex and CA1 region of the hippocampus
    B. Subiculum and amygdala
    C. Basal nucleus of Meynert and substantia nigra
    D. Thalamus and hypothalamus

16. **Which of the following diseases is most likely to be associated with myoclonus, alien limb phenomenon, cortical sensory loss, neuronal degeneration in the precentral and postcentral gyrus, and swollen neurons?**
    A. PSP
    B. CBD
    C. MSA
    D. Dementia with Lewy bodies

17. **Which of the following conditions is associated with early falls, square-wave jerks, slowing of vertical saccades, retrocollis, and a "Mickey mouse midbrain"?**
    A. PSP
    B. CBD
    C. MSA
    D. Dementia with Lewy bodies

18. **Which of the following conditions causes rigidity, gait disturbance, and globose neurofibrillary tangles?**
    A. PSP
    B. CBD
    C. MSA
    D. Dementia with Lewy bodies
    E. Progressive multifocal leukoencephalopathy (PML)

19. **A 70-year-old man presented with visual hallucinations, rapid eye movement sleep disorder, and parkinsonism. His autopsy showed loss of neurons in the substantia nigra and basal nucleus of Meynert, granulovacuolar degeneration in the hippocampus, neurofibrillary tangles, and senile plaques. Which of the following diagnoses is most likely?**
    A. Alzheimer disease
    B. CBD
    C. MSA
    D. Dementia with Lewy bodies
    E. Amyotrophic lateral sclerosis (ALS)–parkinsonism–dementia of Guam

20. **Which disease is characterized by $\alpha$-synuclein immunopositive glial intracytoplasmic inclusions found in oligodendrocytes?**
    A. CBD
    B. MSA
    C. Frontotemporal dementia
    D. PML
    E. ALS–parkinsonism–dementia of Guam

21. **In which of the following conditions do patients have atrophy of the frontotemporal regions, depigmentation of the substantia nigra, and loss of anterior roots?**
    A. Dentatorubral–pallidoluysian atrophy (DRPLA)
    B. CBD
    C. MSA
    D. PSP
    E. ALS–parkinsonism–dementia of Guam

22. **Rosenthal fibers are very prominent in which of the following diseases, some forms of which are caused by mutations in the GFAP gene?**
    A. Alexander disease
    B. Canavan disease
    C. Krabbe disease
    D. Niemann–Pick disease type C

23. **Which of the following is most likely to cause hemorrhagic lesions in the putamen?**
    A. Carbon monoxide poisoning
    B. Kernicterus
    C. Methanol poisoning
    D. Nitrous oxide poisoning

24. **A 20-year-old man is bitten by a bat. Three weeks later, he develops fever, headache, confusion, and hydrophobia. He later dies. Which of the following is most likely to be found in the brain?**
    A. Cowdry A bodies
    B. Cowdry B bodies
    C. Lafora bodies
    D. Negri bodies

25. **Which cell population is affected earliest in Huntington disease?**
    A. Interneurons in the cortex
    B. Interneurons in the striatum
    C. Medium spiny neurons in the striatum
    D. Pyramidal cells

26. **What is the term for the eosinophilic spheric structures that store oxytocin and vasopressin in the neurohypophysis?**
    A. Negri bodies
    B. Herring bodies
    C. Hirano bodies
    D. Marinesco bodies

27. **In which of the following conditions are Bunina bodies most likely to be found?**
    A. Polio
    B. Cytomegalovirus (CMV) encephalitis
    C. Rabies
    D. Alzheimer disease
    E. ALS

28. **In which of the following conditions are Cowdry type A inclusion bodies most likely to be found?**
    A. Polio
    B. Herpes simplex virus (HSV) encephalitis
    C. Rabies
    D. Alzheimer disease
    E. ALS

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**29. In which of the following conditions are Cowdry type B inclusion bodies most likely to be found?**

A. Polio
B. HSV encephalitis
C. Rabies
D. Alzheimer disease
E. ALS

**30. In sections stained with H&E, what is the most likely cause of red neurons?**

A. Hypoxia/ischemia
B. A virus
C. A storage disease

**31. Which of the following is most likely to be found in the intradural extramedullary space?**

A. Astrocytoma
B. Ependymoma
C. Oligodendroglioma
D. Schwannoma

**32. In limbic-predominant age-related TAR DNA-binding protein 43 (TDP-43) encephalopathy (LATE), where are the pathologic changes initially seen?**

A. Amygdala
B. Entorhinal cortex
C. Hippocampus
D. Neocortex

**33. Which of the following cysts is most likely to result in sudden death?**

A. Colloid cyst
B. Epidermoid cyst
C. Neurenteric cyst
D. Rathke's cleft cyst

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# NEUROPATHOLOGY

## ANSWERS

**1. C**

In a normal brain, some neurons can be found in the white matter. This is most commonly seen in the temporal lobe.

**2. C**

The cytoskeleton of eukaryotic cells contains actin microfilaments, intermediate filaments, and microtubules. (The intermediate filaments were given this name because their average diameter is between that of actin microfilaments and that of microtubules.)

There are multiple types of intermediate filaments, including vimentin, keratins, desmin, neurofilaments, and GFAP. Immunohistochemical stains of these filaments are useful for identifying tumor type and origin.

Normal ependymal cells stain strongly with vimentin. Ependymal cells line the ventricles. The side of the cell adjacent to the ventricle has cilia and microvilli. Desmosomes connect the cells and create a barrier between the brain and the cerebral spinal fluid. The central canal of the spinal cord is also lined with ependymal cells.

Ependymomas may stain positive for GFAP, which can cause confusion with astrocytic neoplasms. GFAP immunoreactivity in ependymomas tends to occur in the pseudorosettes.[1]

Congo red stains amyloid.

Desmin stains myogenic tissues.

Luxol fast blue stains myelin.

**3. A**

Astrocytes are the most numerous type of glial cell. In general, protoplasmic astrocytes are found in the cortex, and fibrillary astrocytes are found in the white matter.

Astrocytes provide structural support to neurons and contribute to the blood–brain barrier. In response to injury, astrocytes proliferate and swell.

**4. D**

Schwann cells are a type of glial cells of the peripheral nervous system that produce myelin, whereas oligodendrocytes form myelin in the central nervous system.

Microglia are derived from the monocyte/macrophage lineage. They are of mesodermal origin, not neuroepithelial origin. They phagocytose debris and are important in the inflammatory response.

**5. B**

The H&E stain is one of the principal stains in neuropathology. Hematoxylin is a basic blue/purple dye that binds to acidic structures such as nucleic acids. It stains the nucleus of neurons.

**6. B**

Neurons are the cells most sensitive to hypoxic–ischemic injury.

The most sensitive neurons are hippocampal pyramidal cells of Sommer's sector (CA1) and Purkinje cells in the cerebellar cortex, followed by neurons of cortical layers III, V, and VI.

**7. A**

Apoptosis is associated with activation of intracellular proteases.

Rupture of the cell membrane, inflammation, and random DNA degradation occur with necrosis.

Necrosis and apoptosis are both forms of cell death. Necrosis is a disorganized, unintentional, inflammatory process. Apoptosis is an organized, intentional form of cell death.

In necrosis, water flows into the cell. This leads to swelling of the cytoplasm, nucleus, and mitochondria. The cell membrane ruptures, and the cell contents leak into surrounding tissue.

Apoptosis is programmed cell death that ultimately leads to release of cytochrome *c* from mitochondria, activation of a caspase cascade, and fragmentation of DNA at specific locations.

**8. A**

Both Alzheimer type I and Alzheimer type II astrocytes are found in hyperammonemia, but the former are more common in Wilson disease.

**9. D**

Creutzfeldt astrocytes are associated with demyelination. They are *not* characteristic of Creutzfeldt–Jakob disease.

Bergmann glia act as guides for migrating granular cell neurons during cerebellar development.

**10. D**

Tau is a microtubule-associated protein.

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**11. A**

Tau regulates microtubule structure and function. The gene for tau is on chromosome 17. Hyperphosphorylation of tau proteins can cause filaments to tangle. Neurofibrillary tangles are one of the hallmarks of Alzheimer disease.

Neuritic plaques are composed of amyloid and dystrophic neurites. Neuritic plaques contain Aβ peptide, which is a derivative of amyloid precursor protein. The dystrophic neurites contain phosphorylated tau.

**12. E**

Lewy bodies are intraneuronal cytoplasmic inclusions found in patients with Parkinson disease or dementia with Lewy bodies. A Lewy body consists largely of aggregated forms of α-synuclein.

Neurofibrillary tangles, senile plaques, granulovacuolar degeneration, and Hirano bodies are found in patients with Alzheimer disease.

**13. A**

MSA is an α-synucleinopathy. Likewise, Parkinson disease and Lewy body dementia are also classified as α-synucleinopathies.

PSP, CBD, and CTE are tauopathies.

PSP and CBD are 4-repeat tauopathies.

CTE is a neurodegenerative disease that occurs in some patients who have experienced repetitive traumatic brain injury. Like patients with Alzheimer disease (and in aging), patients with CTE can have 3-repeat and 4-repeat tau. In CTE, neurofibrillary tangles tend to be perivascular. The neurofibrillary tangles become more diffuse but tend to occur in the depths of the sulci in the frontal cortex.[2] Abnormal TDP-43 is often present in patients with CTE.

**14. A**

Diffuse plaques contain Aβ peptide, similar to the neuritic plaques in Alzheimer disease, but diffuse plaques are found in elderly patients who have no cognitive impairment.

Multiple pathologic classification systems are used to assess the brains of patients with suspected Alzheimer disease (see Table 20.1).

*Table 20.1* PATHOLOGIC CLASSIFICATION OF ALZHEIMER DISEASE

| CLASSIFICATION SYSTEM | LESIONS USED FOR CLASSIFICATION |
|---|---|
| **CERAD** | **Neuritic plaques** |
| **Braak and Braak** | **Neurofibrillary tangles** |
| **Thal** | **β-Amyloid plaques** |

CERAD, Consortium to Establish a Registry for Alzheimer's Disease.

Neuritic plaques correlate better with cognitive impairment than do diffuse plaques. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) classification is based on the extent of neuritic plaques.

Neurofibrillary tangles tend to occur in specific locations in Alzheimer disease. The Braak and Braak classification is used to assess the distribution of neurofibrillary tangles. Higher Braak scores are seen in patients with dementia related to Alzheimer disease.[2]

The Thal score is determined by the location of β-amyloid plaques. The lowest score corresponds to the presence of β-amyloid plaques solely in the neocortex.

**15. A**

The Braak and Braak score is a pathologic classification scheme for Alzheimer disease that is based on the distribution of neurofibrillary tangles. The lowest score in this classification indicates that neurofibrillary tangles are limited to the transentorhinal cortex and CA1 region of the hippocampus.

Alzheimer disease neuropathologic findings may be characterized by the ABC score, which is a combination of the Thal score determined by *a*myloid location, the *B*raak stage assessing neurofibrillary tangle distribution, and the *C*ERAD score describing the quantity of neuritic plaques.[2]

**16. B**

Corticobasal degeneration causes asymmetric atrophy of the parasagittal perirolandic cortices. There is neuronal loss and astrocytosis in the primary motor and sensory cortices, substantia nigra, and basal ganglia. There are neuronal and glial lesions containing tau. Astrocytic plaques are found in the cortex. There are tau-positive coiled bodies within oligodendrocytes. Also, swollen, achromatic neurons are seen.

**17. A**

PSP causes selective atrophy of the midbrain tegmentum with relative preservation of the cerebral peduncles and tectum. This resembles the head of Mickey Mouse midbrain on axial magnetic resonance imaging.

Early oculomotor abnormalities in patients with PSP include slowed vertical saccadic movements, hypometric saccades, decreased blinking, and square-wave jerks. Later, supranuclear vertical gaze palsy occurs. Typically, downgaze is affected first. Also, patients have lid retraction, rare blinking, and eyelid apraxia. Late oculomotor findings include supranuclear horizontal gaze palsy.

**18. A**

PSP causes atrophy of the midbrain tegmentum. Sometimes the pons is affected as well. Neurofibrillary tangles and neuropil threads are found in the brainstem and basal ganglia. Globose neurofibrillary tangles are characteristic of PSP. Tuft-shaped astrocytes are also characteristic.

**19. D**

Dementia with Lewy bodies causes diffuse cortical atrophy. The substantia nigra and locus coeruleus become pale. Lewy bodies are found in the cortex and brainstem. These are immunoreactive for α-synuclein, ubiquitin, and neurofilament. Neuritic plaques and neurofibrillary tangles may be seen, as in patients with Alzheimer disease.

**20. B**

In patients with MSA, glial intracytoplasmic inclusions that stain for α-synuclein are found in oligodendrocytes (see Table 20.2).

*Table 20.2* PATHOLOGIC CLASSIFICATION OF NEURODEGENERATIVE DISEASE

| CLASSIFICATION | DISORDER |
|---|---|
| **Tauopathies** | **Alzheimer disease, PSP, CBD, FTD (Pick disease)** |
| **α-Synucleinopathies** | **Parkinson disease, dementia with Lewy bodies, MSA** |

CBD, corticobasal degeneration; FTD, frontotemporal dementia; MSA, multiple system atrophy; PSP, progressive supranuclear palsy.

CBD is characterized by swollen, achromatic neurons; astrocytic plaques in the cortex; and tau-positive coiled bodies in oligodendrocytes.

Frontotemporal dementia (formerly known as Pick disease) is associated with frontotemporal lobar degeneration (FTLD). There is atrophy of the frontal and temporal lobes. There may be relative sparing of the posterior superior temporal gyrus, and the hippocampus is often spared initially.[2] Pick bodies are found in the mesial temporal lobe, especially in the dentate granule cells. These are argyrophilic intracytoplasmic inclusions composed of polymerized tau. Pick cells are neurons with neurofilament in the cytoplasm.

FTLD is associated with multiple proteinopathies. These include tauopathies, TDP-43 proteinopathies, and FET-related proteins. FET-related proteins include FUS, EWSR1, and TAF15. Most familial FTLD is due to mutations in microtubule-associated protein tau (*MAPT*), progranulin gene (*GRN*), or chromosome 9 open reading frame 72 (*C9orf72*).[2] Mutations in *MAPT* are associated with tauopathy pathology. Mutations in *GRN* are associated with TDP-43 pathology. Likewise, expansion of the hexanucleotide GGGGCC repeat in *C9orf72*, which can result in frontotemporal dementia or ALS, is associated with TDP-43 pathology.[3]

Atypical astrocytes with bizarre, pleomorphic nuclei are found in PML. Also in PML, oligodendrocytes have ground-glass intranuclear inclusions due to JC virus.

**21. E**

Patients with ALS–parkinsonism–dementia of Guam have atrophy of the frontotemporal regions, depigmentation of the substantia nigra, and loss of anterior roots.

**22. A**

Rosenthal fibers are prominent in Alexander disease. They are also found in tumors such as pilocytic astrocytomas. They occur normally in the pineal gland.

**23. C**

Methanol poisoning causes hemorrhagic lesions in the putamen.

Carbon monoxide poisoning causes bilateral lesions of the globus pallidus.

Kernicterus is associated with changes in the globus pallidus, subthalamus, and Ammon's horn.

Nitrous oxide causes a myeloneuropathy that resembles vitamin $B_{12}$ deficiency.

**24. D**

This patient has rabies, which is characterized by Negri bodies. Negri bodies are eosinophilic cytoplasmic inclusions that are found most often in pyramidal cells of the hippocampus and Purkinje cells.

Lafora bodies are intracytoplasmic inclusions found in patients with Lafora disease, a progressive myoclonic epilepsy.

**25. C**

GABAergic medium spiny neurons in the striatum are affected early in Huntington disease. Pyramidal cells are involved to a lesser extent, and interneurons are relatively spared.

**26. B**

Herring bodies store oxytocin and vasopressin.

Hirano bodies are found in patients with Alzheimer disease.

Marinesco bodies are eosinophilic intranuclear inclusions that are found in the substantia nigra and locus coeruleus with age.

**27. E**

Bunina bodies are intracytoplasmic inclusions found in patients with ALS.

**28. B**

Cowdry A bodies are eosinophilic intranuclear inclusions found in patients with certain infections, such as CMV, herpes, and subacute sclerosing panencephalitis.

Viruses can produce inclusion bodies in the nucleus or cytoplasm of affected cells. Viral intranuclear inclusions are divided into two types. Type A inclusions are larger and surrounded by a clear zone (halo). The majority of viral intranuclear inclusions are type A.

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**29. A**

Cowdry B bodies are eosinophilic intranuclear inclusions found in patients with acute poliomyelitis. Type B inclusions are smaller than type A inclusions and tend to be multiple.

**30. A**

Neurons affected by hypoxia/ischemia appear red on H&E staining.

**31. D**

Of the tumors listed, schwannoma is most likely to occur in the intradural extramedullary space. Neurofibromas and meningiomas also are found in that space.

Astrocytomas, ependymomas, and oligodendrogliomas are intramedullary neoplasms.

Metastases and bone cancers are found in the extradural space.

**32. A**

In addition to being present in some cases of FTLD, TDP-43 has been associated with limbic-predominant age-related TDP-43 encephalopathy (LATE), which is an amnestic dementia syndrome.[3] In LATE, TDP-43 is initially found in the amygdala (stage 1). Then the entorhinal, hippocampus, and dentate cortex are involved (stage 2). In the final stage of LATE (stage 3), pathological changes involve the neocortex.[2]

Many cases of hippocampal sclerosis of aging are associated with LATE.[2] Hippocampal sclerosis associated with temporal lobe epilepsy has different pathologic features and is not associated with TDP-43.

**33. A**

Colloid cysts arise near the foramen of Monro, where they can have a ball-valve effect. There can be acute or recurrent hydrocephalus. Patients may present with headaches of sudden onset, drop attacks, or sudden death.

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# 21.

# NEUROPHARMACOLOGY

## QUESTIONS

1. **What is the term for the effect that a medication has on the body?**
   A. Pharmacodynamics
   B. Pharmacogenomics
   C. Pharmacokinetics
   D. Potency

2. **Which of the following can affect absorption?**
   A. Antacids
   B. Gastric motility
   C. Proton pump inhibitors
   D. All of the above

3. **Fill in the blank: The amount of drug in the body divided by the concentration of the drug in the blood is the ______________________.**
   A. Absorption
   B. Potency
   C. Therapeutic index
   D. Volume of distribution

4. **Which of the following is the most important factor in determining a medication's concentration in the blood?**
   A. Clearance
   B. Half-life
   C. Potency
   D. Therapeutic index
   E. Volume of distribution

5. **True or false?**
   The effectiveness of a medication does *not* depend on its potency.

6. **Which of the following can affect a medication's half-life?**
   A. Volume of distribution
   B. Protein binding
   C. Lipid solubility
   D. Illness
   E. All of the above

7. **Which term best describes the situation in which a specific amount of drug is eliminated per unit time, regardless of the blood concentration?**
   A. Zero-order kinetics
   B. First-order kinetics
   C. Bioavailability
   D. Bioequivalence

8. **Fill in the blank: The loading dose of a medication is calculated by multiplying the target concentration by the _________________________.**
   A. Clearance
   B. Rate of elimination
   C. Volume of distribution

9. **Which of the following medications does *not* undergo biotransformation?**
   A. Gabapentin
   B. Phenytoin
   C. Diazepam
   D. Clopidogrel

10. **For which of the following drugs is the transport mechanism for absorption from the intestine saturable at therapeutic doses?**
   A. Carbamazepine
   B. Gabapentin
   C. Phenytoin
   D. Valproic acid

11. **Which of the following cytochrome (CYP) P450 enzymes is strongly inhibited by grapefruit juice?**
   A. CYP2C9
   B. CYP2C19
   C. CYP2D6
   D. CYP3A4

12. **Which cytochrome P450 enzyme is primarily responsible for metabolizing carbamazepine?**
   A. CYP2C19
   B. CYP2D6
   C. CYP3A4

13. **For patients of Asian background, a standard dose of diazepam may be toxic because of decreased metabolism by which enzyme?**
   A. CYP2C9
   B. CYP2C19
   C. CYP2D6
   D. CYP3A4

14. **Patients with reduced function of which enzyme have a reduced response to clopidogrel?**
   A. CYP2C19
   B. CYP2D6
   C. CYP2E1
   D. CYP3A4

15. **Which of the following is *least* likely to affect carbamazepine metabolism?**

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A. HLA-B*1502 genotype
B. Erythromycin
C. Cyclosporin
D. Fluoxetine
E. Lamotrigine

**16. Which enzyme helps metabolize warfarin and phenytoin and is inhibited by fluconazole and amiodarone?**
A. CYP1A2
B. CYP2C9
C. CYP2C19
D. CYP2D6

**17. Genotype testing to assess metabolism is *least* necessary for which of the following medications?**
A. Warfarin
B. Azathioprine
C. Tetrabenazine
D. Vigabatrin

**18. Which of the following enzymes is responsible for metabolism of codeine (i.e., poor metabolizers have no analgesia from codeine, whereas ultrametabolizers develop opioid intoxication with typical doses of codeine)?**
A. CYP1A2
B. CYP2C9
C. CYP2C19
D. CYP2D6

**19. Which of the following medications is metabolized by uridine 5′-diphospho-glucuronosyltransferases (UGTs)?**
A. Clobazam
B. Clonazepam
C. Lamotrigine
D. Phenytoin

**20. A patient who is taking valproic acid develops hyperammonemia. Which of the following would be the most effective treatment?**
A. Carnitine
B. Citric acid/potassium citrate
C. Lactulose
D. Sodium benzoate

**21. A 7-year-old patient with spastic quadriplegia is implanted with a baclofen pump. What is the mechanism of action for baclofen?**
A. It is a $\text{GABA}_\text{A}$ receptor agonist.
B. It is a $\text{GABA}_\text{B}$ receptor agonist.
C. It is a $\text{GABA}_\text{B}$ receptor antagonist.
D. It is a glycine receptor agonist.

**22. Phenelzine, selegiline, tranylcypromine, and isocarboxacid can all contribute to serotonin syndrome. What is the mechanism?**
A. Increased serotonin release
B. Decreased serotonin metabolism
C. Inhibition of serotonin reuptake
D. They are direct serotonin receptor agonists.

**23. Fill in the blank: Patients who are taking a monoamine oxidase (MAO) inhibitor should avoid _________________.**
A. Arginine
B. Serine
C. Taurine
D. Tyramine

**24. Which of the following medications is *least* likely to cause serotonin syndrome?**
A. Dapsone
B. Doxepin
C. Lithium
D. Ritonavir
E. Tramadol

**25. Which of the following medications would be most helpful in treating serotonin syndrome?**
A. Amantadine
B. Bromocriptine
C. Cyproheptadine
D. Dextromethorphan
E. Tryptophan

**26. Which of the following has antiserotonergic properties?**
A. Bromocriptine
B. Buspirone
C. Chlorpromazine
D. Lysergic acid diethylamide (LSD)
E. Meperidine

**27. Which of the following features is more characteristic of anticholinergic syndrome than of serotonin syndrome?**
A. Absent bowel sounds
B. Mydriasis
C. Tachycardia
D. Tremor
E. Agitation

**28. Which of the following medications is a selective norepinephrine reuptake inhibitor?**
A. Atomoxetine
B. Guanfacine
C. Dextroamphetamine
D. Bupropion

**29. A patient presents with an overdose of benzodiazepines. Which of the following is the most effective treatment?**
A. Flumazenil
B. Fomepizole
C. Naloxone
D. Pralidoxime
E. Physostigmine

**30. Fill in the blank: Opicapone, entacapone, and tolcapone inhibit ________________________.**
A. Acetylcholinesterase
B. Catechol-*O*-methyltransferase (COMT)

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C. MAO-A
D. MAO-B

**31. Which of the following is a muscarinic receptor agonist?**
A. Atropine
B. Pilocarpine
C. Scopolamine
D. Tacrine

**32. Which of the following medications is *least* likely to cause seizures?**
A. Buspirone
B. Isoniazid
C. Lithium
D. Propoxyphene
E. Theophylline

**33. Which of the following medications is *least* likely to cause cardiac rhythm changes?**
A. Clobazam
B. Cenobamate
C. Lacosamide
D. Lamotrigine
E. Rufinamide

**34. Which of the following medications is *least* likely to affect cardiac rhythm?**
A. Amantadine
B. Citalopram
C. Gabapentin
D. Galantamine
E. Tetrabenazine

**35. Which of the following medications is *least* likely to cause peripheral edema?**
A. Amantadine
B. Amitriptyline
C. Gabapentin
D. Lacosamide
E. Pramipexole

**36. Which of the following medications is most likely to cause Lhermitte's sign, ototoxicity, and nephrotoxicity?**
A. Busulfan
B. Cisplatin
C. Cytarabine
D. Ifosfamide
E. l-Asparaginase

**37. Which of the following is *least* likely to cause constipation?**
A. Amitriptyline
B. Benztropine
C. Cannabidiol
D. Clozapine

# NEUROPHARMACOLOGY

## ANSWERS

**1. A**

The term *pharmacodynamics* refers to the effects of a drug on the body, including its mechanism of action.

Pharmacokinetics refers to the effect of the body on the drug. This includes absorption, metabolism, distribution, and elimination.

Pharmacogenomics is the study of the relationship between an individual's genetic background and their response to medication.

Potency is the dose or concentration of a medication that is needed to produce 50% of its maximal effect.

**2. D**

The term *absorption* refers to the quantity of medication that enters the body. It is affected by the rate and degree of transfer into the blood. Multiple factors affect absorption. These include drug concentration, drug formulation, surface area available for absorption, blood flow, gastric motility, pH, drug solubility, and drug binding.

**3. D**

The amount of drug in the body divided by the concentration of the drug in the blood is the volume of distribution. Drugs that stay in the vascular system have a smaller volume of distribution. The volume of distribution is greater if the drug is lipophilic. Multiple factors affect volume of distribution (see Box 21.1).

***Box 21.1*** **FACTORS THAT AFFECT VOLUME OF DISTRIBUTION**

- Age
- Gender
- Pregnancy
- Organ failure
- Protein binding
- Tissue binding
- Edema or other fluid collections
- Drug acidity

**4. A**

Clearance is the major factor affecting drug concentration in the blood. Clearance is defined as the removal of a drug from the body. Clearance of a drug is equal to its rate of elimination divided by the concentration. The dose of the medication, blood flow to the organs, and liver and kidney function affect clearance. Excretion and metabolism are methods by which elimination occurs. Elimination can occur through the liver, kidneys, lungs, and other organs. Excretion is the removal of a drug through body waste.

The therapeutic index is the ratio of the median effective dose to the median toxic dose.

**5. True**

The effectiveness of a medication does not depend on its potency but, rather, on its maximal efficacy. Maximal efficacy is the maximal response that can be produced by a drug.

**6. E**

Half-life is the time required for the amount of drug in the body to be reduced by half. Half-life depends on the volume of distribution and the clearance of the drug. Therefore, factors that affect volume of distribution or clearance can affect the half-life.

**7. A**

In first-order kinetics, the rate of elimination is proportionate to the concentration. The metabolism is linear: A constant fraction of the drug is metabolized in a given amount of time. Most drugs exhibit first-order kinetics.

In zero-order kinetics, the rate of elimination is constant. This is nonlinear metabolism: The amount of drug eliminated in a given amount of time does not depend on the concentration of the drug.

Phenytoin demonstrates first-order kinetics at lower concentrations. However, at higher concentrations, saturation of hepatic enzymes occurs, and there is a change to zero-order kinetics. Therefore, the clearance of phenytoin depends on its concentration. Aspirin and ethanol also have capacity-limited elimination and demonstrate zero-order kinetics.

Bioavailability refers to the fraction of drug that is absorbed (i.e., not affected by first-pass elimination). Intravenous dosing results in the highest bioavailability.

Bioequivalence refers to the condition in which two drugs with the same active ingredient have similar bioavailability and physiologic effect.

**8. C**

A loading dose of a medication is the product of the target concentration and the volume of distribution.

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**9. A**

Biotransformation is the conversion of a drug into a water-soluble compound for the purpose of excretion. Phase I and phase II reactions make the compound more polar. Phase I reactions include hydrolysis, oxidation, and reduction. Conjugation occurs in phase II reactions. Not all medications undergo biotransformation. Gabapentin and pregabalin, both of which bind to calcium channel $\alpha_2\delta$ subunits, do not undergo biotransformation. They are not metabolized.

In 2019, the U.S. Food and Drug Administration (FDA) issued a warning about the possibility of serious breathing problems in patients taking gabapentin or pregabalin who have respiratory risk factors. Patients at risk include those taking opioid pain medications or other central nervous system depressants and patients with decreased lung function. The elderly were also mentioned as having increased risk.[1]

**10. B**

Gabapentin has saturable absorption at therapeutic doses, which results in nonlinear pharmacokinetics. Gabapentin, which has a structure resembling an amino acid, is transported by a low-capacity L-amino acid transporter in the small intestine. At higher doses, the bioavailability of gabapentin decreases as a result of saturation of this transporter. Therefore, the bioavailability of gabapentin is dose dependent. The bioavailability of gabapentin is also affected by antacids.

Gabapentin has unique pharmacokinetics. It has saturable absorption at therapeutic doses, it is not bound to plasma proteins, and it is not metabolized. It is excreted unchanged in the urine.

Phenytoin and carbamazepine have poor absorption from the gastrointestinal tract, especially in young children.

At therapeutic doses, protein binding of valproic acid is saturable.

**11. D**

CYP3A4 is inhibited by grapefruit juice.

**12. C**

Carbamazepine is primarily metabolized by CYP3A4. Carbamazepine induces CYP3A4 and its own metabolism, resulting in nonlinear pharmacokinetics. It also induces metabolism of oral contraceptives (OCPs), increasing the risk for pregnancy.

Cenobamate is also a CYP3A4 inducer and can reduce levels of OCPs. Other medications that induce the metabolism of OCPs include felbamate, phenobarbital, phenytoin, primidone, and rufinamide. Higher doses of topiramate and oxcarbazepine are also associated with lower OCP levels. Gabapentin, lacosamide, lamotrigine, levetiracetam, pregabalin, valproic acid, vigabatrin, and zonisamide do not lower OCP levels. Folate is recommended for menstruating females who are taking any anti-seizure medication.

Vitamin D levels are also a concern in patients taking anti-seizure medication, especially in those taking enzyme inducers, such as carbamazepine.

**13. B**

Patients of Asian background may have reduced activity of CYP2C19, which is responsible for metabolism of diazepam.

**14. A**

Patients with reduced function of CYP2C19 have a reduced response to clopidogrel. There is also a variant that causes an increased response, resulting in an increased risk for bleeding.

**15. E**

Lamotrigine is least likely to affect carbamazepine metabolism.

Asians with the HLA-B*1502 genotype are more likely to develop Stevens–Johnson syndrome from carbamazepine. Patients can be screened for this genotype before being prescribed carbamazepine.

Erythromycin, cyclosporine, and fluoxetine are inhibitors of CYP3A4, which metabolizes carbamazepine.

**16. B**

CYP2C9 is involved in the metabolism of warfarin and phenytoin. CYP2C19 also plays an important role in metabolism of phenytoin.

**17. D**

Vigabatrin is not metabolized.

Azathioprine is methylated by thiopurine methyltransferase (TPMT). Some patients have reduced or absent TPMT, which results in increased myelotoxicity. Genotyping helps identify these patients.

Tetrabenazine is metabolized by CYP2D6. The activity of this enzyme varies by genotype.

Metabolism of warfarin is also affected by genotype. For example, certain variants of CYP2C9 and vitamin K epoxide reductase complex, subunit 1 (VKORC1) are associated with slow warfarin metabolism.

**18. D**

CYP2D6 metabolizes multiple medications, including codeine, amitriptyline, atomoxetine, dextromethorphan, tetrabenazine, and haloperidol. Inhibitors of CYP2D6 include fluoxetine, paroxetine, and quinidine.

**19. C**

UGTs perform glucuronidation, which is a type of phase II reaction. Lamotrigine is one of the medications metabolized by UGTs. Valproic acid inhibits glucuronidation of lamotrigine, leading to an increase in its half-life.

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**20. A**

Carnitine is used in the treatment of hyperammonemia due to valproic acid. Valproic acid use can deplete carnitine, which is important in its metabolism. Carnitine is a cofactor in the β-oxidation of fatty acids.

Risk factors for hyperammonemia due to valproic acid include hepatic dysfunction, carnitine deficiency, urea cycle disorders, infancy, polypharmacy, and poor nutritional status. Also, the combination of topiramate and valproic acid can produce hyperammonemia, which may be associated with encephalopathy.

Valproic acid is contraindicated in patients with inborn errors of metabolism. For instance, it is contraindicated in urea cycle disorders (e.g., ornithine transcarbamylase deficiency), carnitine deficiency, and mitochondrial diseases. Mitochondrial β-oxidation is one of the pathways by which valproic acid is metabolized. There is an increased risk for liver failure and death in patients with mutations in the mitochondrial DNA polymerase γ (POLG) gene who take valproic acid.

**21. B**

Baclofen is a $\text{GABA}_B$ receptor agonist. Side effects of baclofen include hypotonia, drowsiness, nausea, headache, and dizziness.

Intrathecal baclofen overdose can cause somnolence, cephalad progression of hypotonia, seizures, hypotension, and respiratory depression. Coma can occur.

Signs of withdrawal from intrathecal baclofen include pruritus, paresthesias, muscle rigidity, fever, seizures, altered mental status, and diaphoresis. Rhabdomyolysis and multiple organ failure can occur.

**22. B**

Phenelzine, selegiline, tranylcypromine, and isocarboxacid are MAO inhibitors, which decrease serotonin metabolism. Serotonin is metabolized by MAO to 5-hydroxyindole acetaldehyde, which is then metabolized by aldehyde dehydrogenase to 5-hydroxyindoleacetic acid.

Linezolid, which is an MAO-A inhibitor, also increases serotonin levels due to reduced metabolism.

**23. D**

Patients who are taking an MAO inhibitor should avoid tyramine. MOA enzymes in the intestine and liver digest tyramine. If tyramine metabolism is inhibited by an MAO inhibitor, tyramine accumulates in adrenergic nerves. This results in release of norepinephrine and epinephrine, which can cause a hypertensive crisis. Tyramine can be found in alcoholic beverages, cured meats, and "aged" foods such as cheese. Patients taking nonselective MOA inhibitors and MAO-A inhibitors are at higher risk than those taking MAO-B inhibitors. However, at higher doses, MAO-B inhibitors, such as selegiline, can inhibit both MAO-A and MAO-B.

Sympathomimetic medications should also be avoided to prevent hypertensive crisis.

The combination of an MAO inhibitor and a serotonin reuptake inhibitor can result in serotonin syndrome.

**24. A**

Dapsone is the least likely to cause serotonin syndrome. It can cause methemoglobinemia.

Doxepin, lithium, ritonavir (which is used to treat human immunodeficiency virus infection), and tramadol can increase serotonin levels. Triptans can as well.

**25. C**

Tryptophan increases serotonin synthesis and should be avoided in serotonin syndrome. Amantadine, bromocriptine, and dextromethorphan also can worsen serotonin syndrome.

Serotonin syndrome is treated with removal of the contributing agent or agents and supportive care, including intravenous fluids and treatment of fever. Benzodiazepines have been used to treat serotonin syndrome. Also, cyproheptadine, which is a nonspecific serotonin receptor blocker, has been used.

**26. C**

Chlorpromazine has antiserotonergic properties. The others are serotonergic. Bromocriptine increases serotonin activity. Buspirone and LSD are serotonin receptor agonists. Meperidine prevents serotonin reuptake.

**27. A**

Patients with anticholinergic syndrome have dry skin, normal deep tendon reflexes, and absent bowel sounds. Diarrhea, hyperreflexia, and diaphoresis are seen in serotonin syndrome.

Neuroleptic malignant syndrome (NMS) and serotonin syndrome have similar symptoms, but NMS has a slower progression of symptoms and is characterized by decreased movement rather than hyperkinetic activity. Pupillary dilation and diarrhea are more suggestive of serotonin syndrome than of NMS.

Clonus and myoclonus are also suggestive of serotonin syndrome rather than NMS or anticholinergic syndrome.

**28. A**

Atomoxetine is a selective norepinephrine reuptake inhibitor.

Like clonidine, guanfacine is an $\alpha_2$ agonist. It has been used to treat attention-deficit/hyperactivity disorder because of its action in the prefrontal cortex.

Amphetamine and dextroamphetamine increase release of monoamines (norepinephrine, serotonin, and dopamine), interfere with monoamine reuptake, and inhibit MAO.

Bupropion is a norepinephrine and dopamine reuptake inhibitor.

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## 29. A

Flumazenil, which is a benzodiazepine antagonist, is used in benzodiazepine overdose. However, it can cause seizures due to benzodiazepine withdrawal.

Fomepizole is used to treat methanol or ethylene glycol poisoning.

Naloxone is an opioid antagonist. It can cause withdrawal in patients with opioid dependence.

Pralidoxime is used in organophosphate poisoning. It regenerates active acetylcholinesterase that had been involved in an organophosphorus–cholinesterase complex.

Physostigmine is a cholinesterase inhibitor that is used to treat anticholinergic poisoning. It should not be used if there is prolongation of the PR, QRS, or QTc interval.

## 30. B

Opicapone, entacapone, and tolcapone inhibit COMT, which converts dihydroxyphenylacetic acid (DOPAC) to homovanillic acid. DOPAC is a metabolite of dopamine. COMT inhibitors have been used to treat Parkinson disease. Tolcapone can cause liver toxicity.

## 31. B

Pilocarpine is a muscarinic receptor agonist. It is used to treat dry mouth in patients with Sjögren syndrome and in those who have received chemotherapy. It is also used to treat glaucoma.

Atropine and scopolamine are antagonists to the muscarinic receptor; they block the effect of acetylcholine. Atropine counteracts vagal tone to the heart, causing tachycardia at higher doses. It results in dry mouth, decreased sweating, decreased secretions in the respiratory tract, dilated pupils, and decreased gastrointestinal motility. At higher doses, it can cause hallucinations and restlessness.

Tacrine and donepezil are anticholinesterase agents.

## 32. A

Buspirone is least likely to cause seizures. Bupropion can cause seizures at therapeutic doses. Isoniazid, lithium, propoxyphene, and theophylline also lower the seizure threshold.

## 33. A

Clobazam is least likely to cause changes in cardiac rhythm.

Lacosamide can prolong the PR interval and rarely causes atrioventricular (AV) block. Pregabalin can also prolong the PR interval.

Cenobamate and rufinamide can both shorten the QT interval. They should be avoided in patients with familial short QT syndrome.

Lamotrigine has a warning regarding cardiac rhythm and conduction abnormalities. There is concern that it could slow ventricular conduction and cause arrhythmia.[2]

## 34. C

Patients with long QT syndrome are advised not to take amantadine, citalopram, galantamine, or tetrabenazine. Galantamine can also cause bradycardia and AV block.

Gabapentin is least likely to cause cardiac rhythm changes.

## 35. D

Lacosamide is the least likely to cause peripheral edema.

Amantadine, amitriptyline, gabapentin, pregabalin, and pramipexole can cause peripheral edema.

## 36. B

Cisplatin can cause Lhermitte's sign, ototoxicity, and nephrotoxicity.

Busulfan can cause electroencephalogram abnormalities and generalized seizures.

Cytarabine causes cerebellar dysfunction.

Ifosfamide can cause encephalopathy, which can be treated with methylene blue.

L-Asparaginase can cause venous sinus thrombosis.

## 37. C

Amitriptyline, benztropine, and clozapine have anticholinergic activity and can cause constipation.

Clozapine, which is a treatment for schizophrenia, can cause constipation that can be fatal. In 2020, the FDA strengthened its warning about this.[3] Clozapine has black box warnings for agranulocytosis, seizures, myocarditis, cardiovascular and respiratory effects (e.g., orthostatic hypotension), and increased mortality in elderly patients with dementia-related psychosis.[4] In general, there is an increased risk for death in the elderly treated with antipsychotic drugs.

Cannabidiol (Epidiolex) can cause loose stools.

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# 22.

# NEUROPHYSIOLOGY

## QUESTIONS

1. **Fill in the blank: At rest, the axonal membrane of a nerve is ____________________ when the inside is compared to the outside.**
   A. Negatively polarized
   B. Positively polarized
   C. Neutral

2. **Fill in the blank: The resting membrane potential of the axonal membrane is closest to the equilibrium potential for ______________________.**
   A. Calcium
   B. Chloride
   C. Potassium
   D. Sodium

3. **Fill in the blank: The concentration of ______________________ is greater inside the axonal membrane of the nerve than outside it.**
   A. Chloride
   B. Potassium
   C. Sodium

4. **What is the mechanism of action of 4-aminopyridine, which has been used in patients with multiple sclerosis?**
   A. Calcium channel blocker
   B. Chloride channel blocker
   C. Potassium channel blocker
   D. Sodium channel blocker

5. **What is the function of myelin?**
   A. It reduces the capacitance of the nerve.
   B. It increases the capacitance of the nerve.
   C. It decreases transmembrane resistance.

6. **How does depolarization occur in myelinated nerves?**
   A. It occurs transversely across the diameter of the nerve underneath the myelin sheath.
   B. It occurs longitudinally along the nerve underneath the myelin.
   C. It occurs at gaps in the myelin.

7. **Which of the following nerve types conducts the fastest?**
   A. A large myelinated nerve
   B. A small myelinated nerve
   C. A large unmyelinated nerve
   D. A small unmyelinated nerve

8. **Which of the following is required at the presynaptic neuron for an action potential to result in release of neurotransmitters into the synaptic cleft?**
   A. Calcium influx
   B. Zinc efflux
   C. Potassium influx
   D. Acetylcholine binding

9. **Fill in the blank: At the neuromuscular junction, when acetylcholine binds to the postsynaptic acetylcholine receptor, there is ______________________, which results in depolarization.**
   A. An influx of sodium
   B. An influx of potassium
   C. An influx of chloride
   D. An efflux of calcium

10. **Fill in the blank: In the monosynaptic stretch reflex, ______________________ excites ______________________, which synapse on the anterior horn cells that innervate the muscle that was stretched, causing muscle contraction.**
    A. Stretch of a muscle spindle excites group Ia sensory afferent axons
    B. Stretch of a nuclear chain excites group II afferent fibers
    C. Stretch of Golgi tendon organs excites C fibers
    D. Stretch of Pacinian corpuscles excites Aδ fibers

11. **A 30-year-old woman is scheduled for electromyography (EMG) and nerve conduction studies (NCSs). Her extremities are found to be cold. Which of the following could result from the cold temperature?**
    A. Slowed conduction velocities
    B. Prolonged distal latencies
    C. Increased duration of the motor unit action potential (MUAP)
    D. All of the above

12. **True or false?**
    Unmyelinated (C) fibers are *not* tested with standard nerve conduction studies.

13. **Which nerve conduction studies (NCSs) record the largest nerve fibers?**
    A. Motor NCSs
    B. Sensory NCSs
    C. Mixed NCSs

14. **A child is diagnosed with Guillain–Barré syndrome (GBS)/acute inflammatory demyelinating polyradiculopathy (AIDP). Which of the following is *not* expected on EMG/NCSs?**
    A. Early involvement of the sural nerve sensory action potential

B. Prolonged F waves
C. Slowed conduction velocities
D. Prolonged distal latencies

**15. A patient presents with acute leg weakness and decreased deep tendon reflexes. Conduction velocities are slow, and a demyelinating polyneuropathy is suspected. Which of the following differentiates acquired demyelinating polyneuropathy from hereditary demyelinating neuropathies?**
A. Prolonged distal latencies
B. Prolonged F waves
C. Slow conduction velocities
D. Conduction block

**16. Which of the following statements is *false*?**
A. Excluding technical factors, low-amplitude sensory nerve action potentials (SNAPs) are indicative of a peripheral nerve disorder.
B. SNAPs are normal in a patient who has a radiculopathy.
C. The nerve conduction velocity is determined by the fastest conducting fibers.
D. Abnormal motor conduction studies localize to the peripheral nerve.

**17. Which of the following findings is most consistent with myopathy?**
A. Large, polyphasic motor unit action potentials
B. Pseudoconduction block
C. Small, short-duration motor unit potentials
D. Satellite potentials

**18. Testing of which muscles helps determine whether an ulnar nerve lesion is located proximal to the elbow or at the wrist?**
A. Abductor digiti minimi and flexor pollicis brevis
B. Adductor pollicis and flexor digiti minimi
C. Flexor carpi ulnaris and flexor digitorum profundus
D. Flexor pollicis brevis and flexor digiti minimi

**19. If there appears to be conduction block of the ulnar nerve at the elbow and no other abnormalities are found on EMG/NCSs, which of the following needs to be considered?**
A. Martin–Gruber anastomosis
B. Charcot–Marie–Tooth disease
C. An accessory ulnar nerve
D. Vitamin $B_{12}$ deficiency

**20. A Martin–Gruber anastomosis occurs when there is a branch from the ______________________ nerve to the ______________________ nerve in the forearm.**
A. Median nerve to the posterior interosseous nerve
B. Median nerve to the ulnar nerve
C. Radial nerve to the ulnar nerve
D. Ulnar nerve to the radial nerve

**21. Which of the following statements aids in differentiating an L5 radiculopathy from a peroneal neuropathy?**
A. EMG of the gluteus medius and tensor fascia lata are abnormal in an L5 radiculopathy.
B. EMG of the iliopsoas is abnormal in an L5 radiculopathy.
C. EMG of the gastrocnemius is abnormal in an L5 radiculopathy.
D. EMG of the tibialis anterior is abnormal in a peroneal neuropathy.

**22. When do very slow nerve conduction velocities (<35 m/s in the arms, <30 m/s in the legs) *not* indicate a demyelinating lesion?**
A. In regenerating nerve fibers after complete transection
B. In hereditary peripheral nerve diseases
C. In the hyperacute period of an axonal lesion

**23. True or false?**
Routine motor nerve conduction studies are often normal in postsynaptic disorders of the neuromuscular junction (NMJ).

**24. True or false?**
A positive edrophonium test is specific for myasthenia gravis (MG).

**25. What is the most sensitive test for myasthenia gravis?**
A. Rapid repetitive nerve stimulation
B. Slow repetitive nerve stimulation
C. Single-fiber EMG

**26. An intravenous drug user presents with vomiting and abdominal pain. He has diplopia and blurred vision. On examination, he has impaired accommodation. He develops ophthalmoplegia, areflexia, and a flaccid quadriparesis. The weakness progresses rapidly in a descending pattern. What is the EMG most likely to show?**
A. Large, polyphasic motor unit action potentials
B. Complex repetitive discharges
C. An incremental response with rapid repetitive nerve stimulation
D. Absence of insertional activity

**27. Which of the following is most likely to be associated with a "dive bomber" sound on EMG?**
A. Duchenne muscular dystrophy
B. Oculopharyngeal muscular dystrophy
C. Facioscapulohumeral muscular dystrophy
D. Myotonic dystrophy

**28. Which of the following types of discharges are most likely to be found in hyperkalemic periodic paralysis, myotubular myopathy, and polymyositis?**
A. Complex repetitive discharges
B. Myokymic discharges
C. Myotonic discharges
D. Neuromyotonic discharges

**29. In which metabolic disease are myotonic discharges most likely to occur?**
A. Acid maltase deficiency
B. Metachromatic leukodystrophy

C. Krabbe disease
D. Adrenoleukodystrophy

**30. Which of the following can be observed in patients with brainstem neoplasms, multiple sclerosis, or a history of radiation therapy?**

A. Contractures
B. Cramp potentials
C. Myokymic discharges
D. Neuromyotonic discharges

**31. Which of the following are caused by the spontaneous discharge of muscle fibers in near-synchrony and with uniform frequency? (They can be seen in anterior horn cell diseases, muscular dystrophies, and certain normal muscles.)**

A. Complex repetitive discharges
B. Myokymic discharges
C. Myotonic discharges
D. Neuromyotonic discharges

**32. A patient receiving steroids for dermatomyositis presents with worsening weakness. Which of the following statements differentiates steroid myopathy from polymyositis or dermatomyositis?**

A. Myotonic discharges are seen in steroid myopathy.
B. Positive sharp waves are seen in steroid myopathy.
C. Steroid myopathy causes proximal weakness.
D. There is a lack of spontaneous activity on EMG in patients with steroid myopathy.

**33. How much of the cortex must be activated to generate activity on scalp electroencephalography (EEG)?**

A. 3 cm$^2$
B. 6 cm$^2$
C. 15 cm$^2$
D. 20 cm$^2$

**34. Asynchronous sleep spindles are seen in a 1-year-old child. What is the most likely explanation?**

A. Agenesis of the corpus callosum
B. Infantile spasms
C. Ohtahara syndrome
D. This finding is normal in this age group.

**35. A patient is thought to have lambda waves on her EEG. What can be done to verify this?**

A. Ask her to close her eyes; the lambda waves should disappear when she does so.
B. Ask her to move her hands.
C. Wake her up from sleep.
D. Repeat hyperventilation.

**36. A patient undergoes removal of a small right frontal tumor (lesionectomy). An EEG performed 3 months later shows sharp, higher amplitude activity over the right frontal area without epileptiform discharges. What is this activity called?**

A. Bancaud phenomenon
B. Breach rhythm
C. Small sharp spikes
D. Wicket spikes

**37. Which of the following is most closely associated with seizures?**

A. Posterior slow waves of youth
B. Subclinical rhythmic electrographic discharges of adults (SREDA)
C. Temporal intermittent rhythmic delta activity (TIRDA)
D. 14- and 6-Hz positive bursts

**38. True or false?**

Interictal discharges are more prominent in rapid eye movement (REM) sleep than in non-REM sleep.

**39. In which animal model of epilepsy was levetiracetam shown to work?**

A. Maximal electroshock
B. Pentylenetetrazol
C. Kindling

**40. Which of the following findings is *least* consistent with sporadic Creutzfeldt–Jakob disease (CJD)?**

A. Periodic sharp wave complexes occurring every 15 seconds
B. Increased signal in the basal ganglia on magnetic resonance imaging (MRI)
C. Increased signal in the cortical ribbon on MRI
D. Increased 14-3-3, tau, and neuron-specific enolase in the cerebrospinal fluid

**41. On EEG, patients with which of the following conditions are most likely to have prolonged slowing with hyperventilation?**

A. Hypocalcemia
B. Hypoglycemia
C. Hyponatremia
D. Hypomagnesemia

**42. A 15-year-old girl presents for an EEG after her first generalized tonic–clonic seizure. During photic stimulation, she has myoclonic jerks followed by another generalized tonic–clonic seizure. What is the term for this response to photic stimulation?**

A. Photoconvulsive response
B. Photomyogenic response/photomyoclonic response
C. Photoparoxysmal response

**43. A photoparoxysmal response is seen in which of the following conditions?**

A. Dentatorubral–pallidoluysian atrophy (DRPLA)
B. Lafora body disease
C. Neuronal ceroid lipofuscinosis
D. Unverricht–Lundborg disease
E. All of the above

**44. A 20-year-old woman describes her seizure as beginning with a rising feeling in her stomach. Her family says that she then stares, smacks her lips, and performs odd movements with her left hand. Her right hand is in an unusual posture. Where is the seizure most likely beginning?**

A. Left occipital lobe
B. Left temporal lobe
C. Right frontal lobe
D. Right parietal lobe

**45. A baby at 27 weeks corrected gestational age would most likely have which EEG finding?**
A. Tracé discontinu
B. Tracé alternant
C. Activité moyenne
D. Continuous slow-wave sleep during quiet sleep

**46. Delta brushes are seen in premature infants. In which condition are extreme delta brushes most likely to be seen?**
A. Angelman syndrome
B. Anti–*N*-methyl-D-aspartate (NMDA) receptor encephalitis
C. Baclofen overdose
D. Rett syndrome

**47. Periodic discharges are *least* likely to be seen in which of the following conditions?**
A. Subacute sclerosing panencephalitis (SSPE)
B. Stroke
C. Herpes encephalitis
D. West Nile encephalitis

**48. True or false?**
With near-field potentials, the amplitude recorded is higher the closer the recording electrode is to the source.

**49. What is indicated by unilateral prolongation of P100 on a visual evoked potential?**
A. A prechiasmatic lesion of the optic pathway
B. Glaucoma
C. An occipital lesion
D. A lesion in the lateral geniculate nucleus

**50. Somatosensory evoked potentials (SSEPs) evaluate which pathway?**
A. Corticospinal tract
B. Posterior column–medial lemniscal pathway
C. Spinocerebellar tract
D. Spinothalamic tract

**51. Which structure produces wave I on brainstem auditory evoked potentials (BAEPs)?**
A. Cochlear nucleus
B. Cranial nerve VIII (CN 8)
C. Lateral lemniscus
D. Medial geniculate nucleus

**52. What is the term for electrographic activity lasting greater than 10 seconds in duration that does not qualify for a definite seizure but is strongly suspected to be affecting awareness, contributing to clinical symptoms, and/or adding to neuronal injury?**
A. Brief potentially ictal rhythmic discharges (BIRDs)
B. Cyclic alternating pattern of encephalopathy (CAPE)
C. Interictal–ictal continuum
D. WHAM

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# NEUROPHYSIOLOGY

## ANSWERS

**1. A**

At rest, the axonal membrane of a nerve is negatively polarized when the inside is compared to the outside.

**2. C**

The resting membrane potential is closest to the equilibrium potential for potassium.

**3. B**

The resting membrane potential of the nerve results from the presence of a semipermeable membrane and the sodium–potassium ($Na^+/K^+$) pump. The concentrations of potassium and large anions are greater inside the axonal membrane of the nerve than outside it. The $Na^+/K^+$ pump causes sodium to move outside and potassium to move inside. Depolarization results in an influx of sodium. When depolarization occurs, sodium is driven into the cell by the concentration and electrical gradients. Closure of voltage-sensitive sodium channels and opening of voltage-sensitive potassium channels contribute to neuronal repolarization.

The concentrations of chloride and sodium are greater outside the axonal membrane.

**4. C**

The compound 4-aminopyridine is an antagonist to voltage-gated potassium channels (the delayed rectifier potassium channel). It increases the chance that the axon will depolarize.

**5. A**

Myelin reduces the capacitance of the nerve and increases the transmembrane resistance.

**6. C**

In myelinated nerves, depolarization occurs by saltatory conduction. Depolarization occurs at the nodes of Ranvier, gaps where the nerve is not myelinated. The highest density of sodium channels is at the nodes of Ranvier.

**7. A**

Conduction velocity of a nerve depends on its diameter and whether it is myelinated. Large nerves have less electrical resistance than small nerves and conduct faster. Myelinated nerves conduct faster than unmyelinated nerves. Less nerve membrane is depolarized in myelinated nerves because of saltatory conduction. The action potential travels from node to node rather than continuously along the nerve. More current is needed for saltatory conduction.

**8. A**

At the synapse, exocytosis of a synaptic vesicle depends on calcium influx. Synaptotagmin acts as a calcium sensor on the vesicle.

The term *quanta* refers to the number of neurotransmitter molecules within a single vesicle. Spontaneous release of a single quanta of acetylcholine produces a miniature endplate potential.

The term *quantal content* refers to the number of synaptic vesicles released by the action potential. It is determined by the number of synaptic vesicles available at the presynaptic terminal multiplied by the probability of quantal release.

**9. A**

Two acetylcholine molecules must bind to each subunit of the acetylcholine receptor to open the channel. When the channel opens, there is an influx of sodium. This results in depolarization and an endplate potential (EPP). The size of the EPP depends on the amount of acetylcholine that binds to the receptor. If the EPP is above the muscle membrane's threshold, a muscle fiber action potential is generated.

**10. A**

In the monosynaptic stretch reflex, stretch of a muscle spindle excites group Ia sensory afferent axons. These synapse on the anterior horn cells that innervate the muscle that was stretched, causing muscle contraction.

**11. D**

Cold temperature results in slowed conduction velocities and prolonged distal latencies. Also, amplitude and duration of potentials are increased on NCSs. Sensory nerve action potentials (SNAPs) are more affected than compound muscle action potentials (CMAPs). In addition, motor unit action potentials (MUAPs) are increased in duration and amplitude and have more phases on EMG.

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**12. True**

Small myelinated (Aδ, β) and unmyelinated (C) fibers are *not* tested with standard NCSs. Unmyelinated fibers carry pain, temperature, and autonomic information.

**13. C**

The largest and fastest nerve fibers are the Ia fibers. Ia fibers mediate the afferent limb of the muscle stretch reflex. Ia fibers are assessed in mixed nerve studies but not in pure motor or pure sensory NCSs, so mixed nerve studies are faster than routine NCSs. These fibers also have the greatest amount of myelin. They are affected early by demyelinating lesions. Therefore, mixed nerve studies are typically more sensitive to demyelination than routine NCSs. For example, a palmar mixed nerve study may detect carpal tunnel syndrome before routine NCS.

**14. A**

The sural sensory response tends to be spared in GBS/AIDP, even when other sensory responses are affected.

Initially, routine motor NCS may be normal. Typically, the earliest finding in GBS is delayed or absent F waves and H responses. Later, prolonged distal latencies, conduction block, and temporal dispersion are seen.

Low-amplitude CMAPs predict a poor prognosis in GBS. These can occur with distal conduction block or axonal loss.

The axonal variants of GBS are acute motor axonal neuropathy (AMAN) and acute motor sensory polyneuropathy (AMSAN). These tend to progress more rapidly than typical GBS. Patients with AMAN or AMSAN may require ventilation and may have dysautonomia. AMAN is often associated with *Campylobacter jejuni* infection. Porphyria is also an acute axonal polyneuropathy and should be included in the differential diagnosis of AMAN and AMSAN.

**15. D**

Conduction block, temporal dispersion, and abnormal phase cancellation occur in acquired demyelinating polyneuropathy because of the variable degrees of demyelination. They do *not* occur in hereditary demyelinating neuropathies; patients with these conditions have uniform conduction slowing. Hereditary demyelinating neuropathies and acquired demyelinating polyneuropathy are both associated with prolonged distal latencies, prolonged F waves, prolonged H waves, and slow conduction velocities.

**16. D**

An abnormal motor NCS does not necessarily localize to the peripheral nerve. It can be abnormal with anterior horn cell, nerve root, neuromuscular junction, or muscle lesions. In contrast, low-amplitude SNAPs do indicate a peripheral nerve disorder.

A patient may have sensory loss with normal SNAPs if the lesion is proximal to the dorsal root ganglia, if there is a proximal demyelinating lesion, or if there is a hyperacute axonal loss lesion.

In patients with brain lesions, spinal cord lesions, or radiculopathies, the SNAPs are normal because the lesion is proximal to the dorsal root ganglia. Because SNAPs are normal in radiculopathy and abnormal in plexopathy, they are helpful in differentiating the two conditions. Patients with a radiculopathy may have sensory loss with normal SNAPs. However, EMG studies may show neuropathic changes in the paraspinal muscles in a patient with radiculopathy.

**17. C**

Small, short-duration motor unit action potentials on EMG are consistent with myopathy. In acute myopathy, short-duration, small-amplitude polyphasic MUAPs are seen. Recruitment is normal or early. (Recruitment refers to the addition of more MUAPs with increased firing rates.) The MUAPs in chronic myopathies may be difficult to differentiate from those of chronic neuropathy on EMG. However, in chronic myopathy, recruitment is normal or early. Sensory NCSs are normal in myopathy. Motor NCSs may be normal in a proximal myopathy because the NCSs usually study distal muscles.

Large, polyphasic MUAPs are consistent with reinnervation. For example, they are seen in motor neuron diseases and in chronic axonal injury.

Immediately after a lesion causing axonal loss, NCS will be normal if stimulation and recording are performed distal to the lesion. Acutely, the only finding on EMG is decreased recruitment in the weak muscles. With chronic axonal injury, decreased recruitment and large, polyphasic MUAPs are seen.

In central nervous system disorders, MUAPs and recruitment are normal; however, there is decreased activation. The ability to increase firing frequency (activation) is a central process.

Satellite potentials can be seen in myopathy and in neuropathy. For example, they are seen in early reinnervation. A satellite potential is a small action potential that consistently follows a main action potential; satellite potentials are time locked.

Pseudoconduction block can occur in the setting of nerve transection or nerve infarction, as seen in vasculitic neuropathy. Pseudoconduction block is seen in acute axonal loss if stimulation is performed both distal and proximal to the lesion. With distal stimulation, the amplitude is normal; with proximal stimulation, the amplitude is reduced. This gives the appearance of a conduction block. However, when the study is repeated later (after Wallerian degeneration), low amplitudes are seen with both proximal and distal stimulation.

**18. C**

If both the flexor carpi ulnaris and flexor digitorum profundus are abnormal with axonal loss, the lesion is proximal to the elbow.

The ulnar nerve innervates multiple muscles in the hand (i.e., abductor digiti minimi, opponens digiti minimi, flexor digiti minimi, third and fourth lumbricals, first dorsal and first palmar interossei, adductor pollicis, and flexor pollicis brevis). It also innervates the flexor carpi ulnaris and the flexor digitorum profundus III and IV in the forearm.

**19. A**

If there appears to be conduction block of the ulnar nerve at the elbow and no other abnormalities are found, a Martin–Gruber anastomosis should be considered.

**20. B**

A Martin–Gruber anastomosis is a connection between the median and ulnar nerves. In patients with this condition, the median nerve innervates muscles typically innervated by the ulnar nerve: the first dorsal interosseous, abductor digiti minimi, and adductor pollicis. Some authorities would also include the deep head of the flexor pollicis brevis.

Anomalous innervation can also occur in the lower extremity. There may be an accessory peroneal nerve innervating the extensor digitorum brevis (EDB). The accessory peroneal nerve is a branch of the superficial peroneal nerve. Typically, the deep peroneal nerve innervates the EDB. The deep peroneal nerve is a branch of the common peroneal nerve.

**21. A**

There are multiple lesions that can cause foot drop. In the peripheral nervous system, these include lesions of the deep peroneal nerve, common peroneal nerve, sciatic nerve, lumbosacral plexus, and L5 nerve root. EMG of the tibialis anterior can be abnormal with any of these lesions. Weakness of ankle inversion in addition to foot drop indicates that the lesion also affects the tibial nerve. Involvement of the tibial and peroneal nerves indicates that the lesion involves the sciatic nerve, lumbosacral plexus, or L5 nerve root. If the gluteus medius and the tensor fascia lata are involved, the patient has a lumbar plexopathy or an L5 radiculopathy. Abnormalities in the paraspinal muscles indicate that the patient has an L5 radiculopathy rather than a lumbar plexopathy.

EMG of the iliopsoas and gastrocnemius muscles should be normal in an L5 radiculopathy (see Table 22.1).

EMG of the tibialis anterior does not help differentiate a peroneal neuropathy from an L5 radiculopathy. It may be abnormal with either lesion.

*Table 22.1* INNERVATION OF SELECTED LOWER EXTREMITY MUSCLES

| MUSCLE | INNERVATION (SPINAL ROOTS) |
|---|---|
| **Iliopsoas** | **L1, L2, L3** |
| **Gluteus medius and tensor fascia lata** | **L4, L5, S1** |
| **Gastrocnemius** | **S1, S2** |

**22. A**

Typically, very slow nerve conduction velocities indicate a demyelinating lesion. An exception occurs in the setting of nerve injury. After complete nerve transection, regenerating nerve fibers can have very slow nerve conduction velocities.

**23. True**

NMJ disorders can be mistaken for myopathy. Sensory conduction studies are normal. Distal latencies, conduction velocities, and late responses are normal on motor studies. Also, CMAP amplitudes are typically normal in postsynaptic disorders such as myasthenia gravis (MG). However, CMAP amplitudes are decreased in presynaptic NMJ disorders such as Lambert–Eaton myasthenic syndrome (LEMS) and botulism. In botulism and LEMS, the number of quanta released is reduced.

Repetitive nerve stimulation helps differentiate an NMJ disorder from a myopathy. Both MG and LEMS show a decrement with 3-Hz stimulation. However, LEMS shows a significant increment with rapid repetitive nerve stimulation or brief intense exercise. Clinically, LEMS is associated with reduced deep tendon reflexes and autonomic dysfunction, which are not typical of MG.

**24. False**

A positive edrophonium test is *not* specific for MG. Amyotrophic lateral sclerosis, LEMS, and brainstem lesions can also result in a positive edrophonium test.

**25. C**

Single-fiber EMG (SF-EMG) is very sensitive for MG but is not specific. SF-EMG of weak muscles demonstrates increased jitter in patients with MG. However, increased jitter can be seen in many other conditions, including myopathic diseases, neuropathic diseases, and other NMJ disorders.

**26. C**

This patient has wound botulism. The rapid progression, decreased reflexes, and autonomic dysfunction help clinically differentiate it from MG.

Botulinum toxin causes reduced CMAPs. Latencies and conduction velocities are normal. Sensory nerve conduction studies are normal. Slow repetitive nerve stimulation can cause a decrement. Rapid repetitive nerve stimulation can cause an incremental response. Lack of an increment does *not* rule out botulism.

In most NMJ disorders, there is no abnormal spontaneous activity. Botulism is the exception. Fibrillation potentials and positive sharp waves, which are signs of denervation, are seen.

Botulism is in the differential diagnosis of AIDP.

**27. D**

Myotonic discharges, as seen in myotonic dystrophy, cause a dive bomber sound on EMG. The discharges wax and wane in amplitude and frequency.

**28. C**

Myotonic discharges can be seen in hyperkalemic periodic paralysis, polymyositis, myotubular myopathy, myotonic dystrophy, myotonia congenita, and paramyotonia congenita.

**29. A**

Myotonic discharges are seen in the paraspinal muscles of patients with acid maltase deficiency.

**30. C**

Myokymic discharges are spontaneous, rhythmic discharges arising from a motor unit. Rippling of the muscle may be seen clinically. These discharges can be seen in cases of radiation-induced nerve damage. They can help differentiate radiation plexitis from neoplastic invasion of the brachial plexus. Facial myokymia can be seen in multiple sclerosis and in brainstem neoplasms.

Contractures are electrically silent on EMG. They can be seen in metabolic diseases, such as glycolytic enzyme defects.

Cramp potentials are rapid discharges of motor axons.

**31. A**

Complex repetitive discharges result from the spontaneous discharge of muscle fibers in near-synchrony and with uniform frequency (see Table 22.2). A single muscle fiber depolarizes, and there is direct spread from it to another muscle membrane (ephaptic spread). Complex repetitive discharges can be seen in anterior horn cell diseases, muscular dystrophies, and certain normal muscles.

*Table 22.2* EMG SPONTANEOUS WAVEFORM SOURCE GENERATORS

| GENERATOR | TYPES OF WAVEFORMS |
|---|---|
| **Motor neuron/axon** | **Cramp, fasciculation, myokymia, neuromyotonia, tetany** |
| **Neuromuscular junction** | **Endplate noise** |
| **Terminal axon** | **Endplate spike** |
| **Multiple muscle fibers** | **Complex repetitive discharges** |
| **Single muscle fiber** | **Fibrillation, myotonia, positive wave** |

Neuromyotonic discharges are seen in Isaac syndrome. In this condition, muscles do not relax; patients have continuous muscle fiber activity. The patient experiences stiffness and muscle cramps. Myokymia can be seen. Patients have delayed muscle relaxation. However, in contrast to patients with myotonia, percussion does not cause muscle contraction. Patients may have hyperhidrosis. Some patients have a malignancy, such as thymoma or small cell lung cancer. Some patients with Isaac syndrome have Morvan syndrome, which is characterized by hallucinations, insomnia, and autonomic dysfunction. Some patients with Morvan syndrome have potassium channel antibodies, and some have thymoma.

**32. D**

Proximal weakness occurs in steroid myopathy, polymyositis, and dermatomyositis. The lack of spontaneous activity on EMG in patients with steroid myopathy helps differentiate it from dermatomyositis and polymyositis. Insertional activity is normal in steroid myopathy. There are no positive sharp waves or fibrillations. Steroid myopathy tends to affect type II fibers. EMG tends to assess type I fibers.

Fibrillations and positive waves are seen in inflammatory myopathies such as polymyositis and dermatomyositis. There are small, short-duration, polyphasic motor units in patients with polymyositis and dermatomyositis.

Just as dermatomyositis and its treatment can each cause myopathy, both HIV and zidovudine can cause myopathy. Zidovudine myopathy is associated with ragged red fibers due to mitochondrial injury. These help differentiate it from HIV myopathy.

**33. B**

To generate activity on a scalp EEG, 6 $cm^2$ of cerebral cortex must be activated. The EEG is generated from the summation of inhibitory and excitatory postsynaptic potentials on the apical dendrites of cortical pyramidal neurons.

Focal epileptiform activity results from a paroxysmal depolarization shift at the cellular level.

Irregular focal slow activity is caused by a focal subcortical lesion or dysfunction.

A cortical lesion can cause focal voltage attenuation.

**34. D**

Asynchronous sleep spindles are normal until age 2 years. Sleep spindles appear at age 2 months but may be asynchronous until age 2 years because of insufficient myelination.

**35. A**

Lambda waves occur during wakefulness. They are positive discharges seen over the occipital region. They occur with scanning and should disappear with eye fixation or closure.

Mu rhythm is seen over the central regions. It is 7- to 11-Hz arch-shaped activity that resolves with movement of the contralateral hand.

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**36. B**

After surgery, a breach rhythm can be seen. This activity is more sharp and higher in amplitude because of the skull defect. Faster frequencies are seen.

Bancaud phenomenon is the term used for unilateral lack of attenuation of the alpha rhythm with eye opening.

Small sharp spikes are a pseudoepileptiform pattern seen in adolescents and adults in sleep.

Wicket spikes are also normal waveforms seen in adults, but they can be mistaken for epileptiform temporal spikes.

**37. C**

TIRDA is most closely associated with an increased risk for seizures.

SREDA is a normal variant seen in adults older than age 50 years.

In children, occipital intermittent rhythmic delta activity (OIRDA) may be seen in patients with childhood absence epilepsy.

The pattern of 14- and 6-Hz positive bursts is a pseudoepileptiform pattern. These bursts can occur in normal adolescents in drowsiness and sleep. They have also been described in Reye syndrome.

Rhythmic mid-temporal theta of drowsiness (previously known as psychomotor variant) is also sometimes mistaken for epileptiform activity.

Posterior slow waves of youth are a normal EEG finding.

**38. False**

Interictal discharges are *less* prominent in REM than in non-REM sleep.

**39. C**

Levetiracetam was shown to be effective in the kindling model of epilepsy.

**40. A**

Periodic sharp wave complexes are seen in sporadic Creutzfeldt-Jakob disease (CJD) but not in variant CJD. The frequency of discharges in CJD is every 0.5 to 1 second.

**41. B**

Hyperventilation is an activation procedure performed during an EEG. Children often have symmetric slowing of the background with hyperventilation. Occasionally, this may be associated with staring. If no epileptiform activity is present, then this finding can be considered normal. Hyperventilation may cause absence seizures in at-risk individuals.

Hypoglycemia may result in prolonged slowing with hyperventilation.

Rebuildup can occur in patients with moyamoya, who should *not* be hyperventilated; impressive slowing is seen a few minutes after hyperventilation has been completed. Hyperventilation can cause decreased carbon dioxide and alkalosis. It may result in vasospasm and decreased cerebral perfusion. Hyperventilation is *contraindicated* in patients with cerebrovascular disease and intracranial hemorrhage. It is also contraindicated in sickle cell disease and trait, congenital heart disease, cystic fibrosis, and active asthma.

Occasionally, tetany can be induced by hyperventilation in patients with hypocalcemia.

**42. A**

The term *photoparoxysmal response* refers to epileptiform activity (without clinical correlate) resulting from photic stimulation. It is classically seen in genetic generalized epilepsies, especially juvenile myoclonic epilepsy. Patients with Dravet syndrome may also have a photoparoxysmal response.

A photoconvulsive response is a clinical seizure resulting from photic stimulation.

A photomyogenic (or photomyoclonic) response occurs when the frontalis muscle contracts in response to photic stimulation; the contractions are time locked with the flashes of light. Risk factors are alcohol withdrawal and barbiturate withdrawal.

**43. E**

A photoparoxysmal response may be seen in any of the conditions listed. Patients with progressive myoclonic epilepsy may have a photoparoxysmal response. Patients with neuronal ceroid lipofuscinosis tend to have a photoparoxysmal response at low frequencies.

**44. B**

This description is consistent with a left temporal lobe seizure. Patients with temporal lobe epilepsy often describe a rising epigastric sensation at the beginning of the seizure. Ipsilateral automatisms and contralateral dystonic posturing are also typical.

**45. A**

Tracé discontinu is the EEG pattern seen in the most premature infants. It is characterized by periods of higher voltage activity separated by periods of low-voltage activity measuring less than 25 microvolts. By 36 weeks, it is seen only during quiet sleep. By term, tracé alternant replaces tracé discontinu in quiet sleep. Tracé alternant resembles tracé discontinu (i.e., higher amplitude activity separated by periods of lower amplitude activity), but the lower voltage activity is greater than 25 microvolts.

**46. B**

Anti-NMDA receptor encephalitis is an autoimmune encephalitis that causes fever, behavioral changes, movement disorders, seizures, and autonomic dysfunction. It is diagnosed by the finding of antibodies to the NMDA

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glutamate receptor in serum or cerebrospinal fluid. (The antibodies are usually to the NR1 subunit.) EEG may show an extreme delta brush pattern. Positron emission tomography may show frontal and temporal hypermetabolism with occipital hypometabolism. Brain MRI may be normal. Some women with anti-NMDA receptor encephalitis have an ovarian teratoma or develop one later.

Baclofen is an $\gamma$-aminobutyric acid type B ($\text{GABA}_B$) receptor agonist. Baclofen overdose can cause multiple EEG abnormalities, including triphasic waves, generalized periodic discharges, and a burst-suppression pattern.

Angelman syndrome causes rhythmic delta activity over the frontal regions.

In Rett syndrome, spikes may be seen over the central head region.

## 47. D

Lateralized period discharges (LPDs), formerly periodic lateralizing epileptiform discharges, are seen in patients with stroke or herpes encephalitis. Stroke is the most common cause, but LPDs are a classic finding in herpes encephalitis.

Sporadic CJD and SSPE cause generalized periodic discharges. The frequency of discharges in CJD is every 0.5 to 1 second. The frequency of discharges in SSPE is every 4 to 15 seconds (see Figures 22.1 and 22.2).

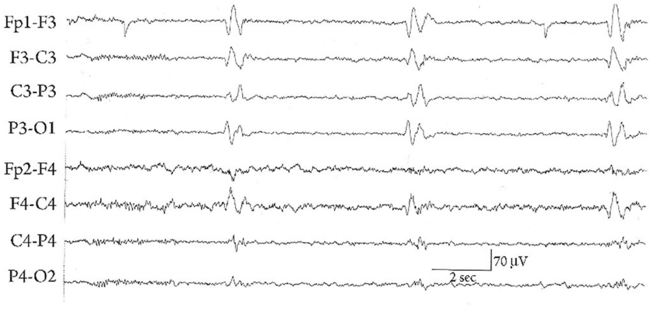

**Figure 22.2** SSPE with periodic discharges. SOURCE: From Misulis KE. *Atlas of EEG, Seizure Semiology, and Management*, Fig. 4-80. New York: Oxford University Press; 2013.

Anoxia can cause generalized periodic discharges or bilateral independent lateralized periodic discharges.

West Nile encephalitis is less likely to cause periodic discharges.

## 48. True

With near-field potentials, the amplitude recorded is higher the closer the recording electrode is to the source. A far-field potential is seen simultaneously at all recording electrodes even though one of them is closer to the source.

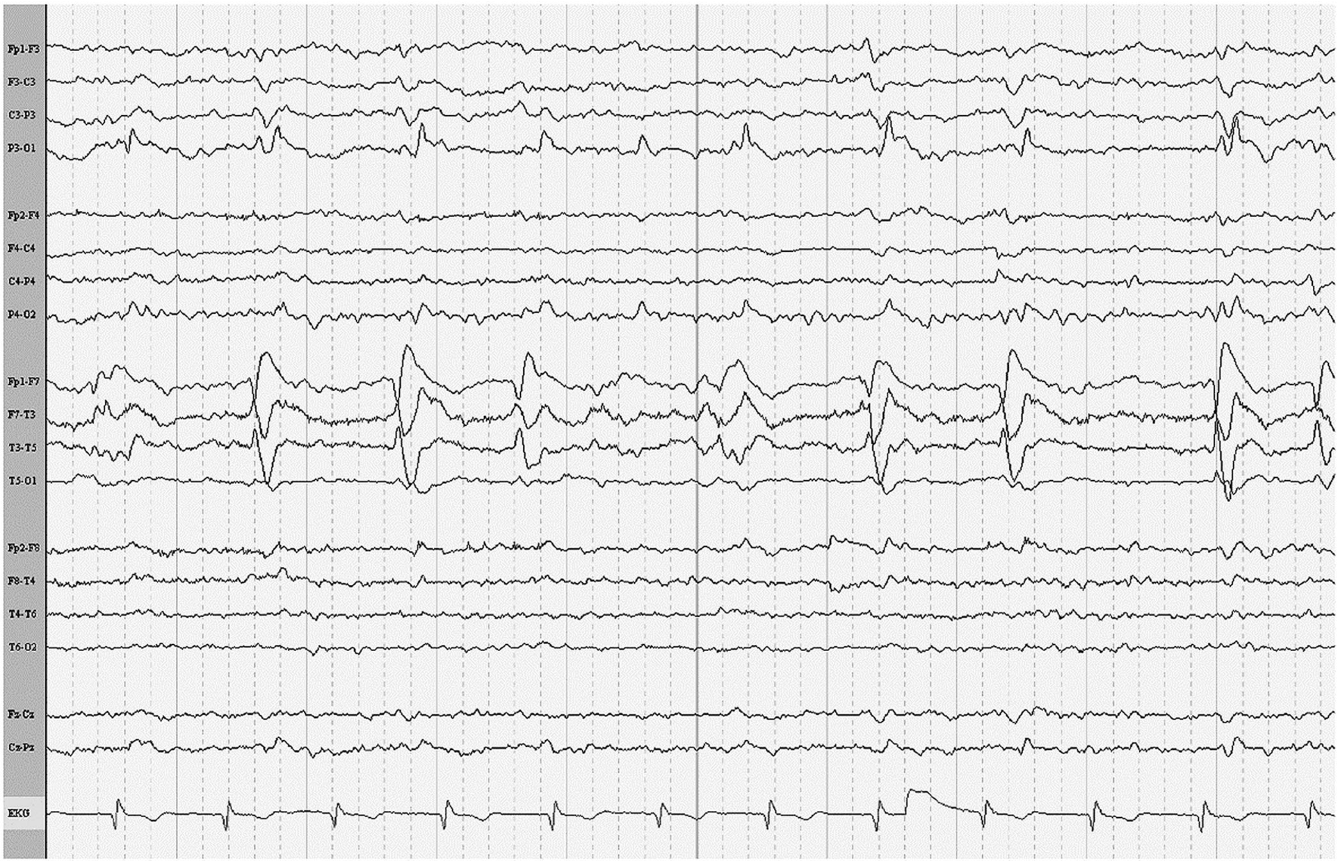

**Figure 22.1** Example of lateralized periodic discharges. SOURCE: From Misulis KE. *Atlas of EEG, Seizure Semiology, and Management*, Fig. 4-73. New York: Oxford University Press; 2013.

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**49. A**

Unilateral prolongation of P100 on visual evoked potential testing indicates a prechiasmatic lesion of the optic pathway. Optic neuritis is one example.

Visual evoked potentials are affected by anesthesia and are not usually tested intraoperatively.

**50. B**

SSEPs evaluate the posterior column–medial lemniscal pathway. Intraoperative SSEPs monitor the integrity of this pathway.

Intraoperative SSEPs can also identify sensorimotor cortex. With the use of median nerve SSEPs, the location of the central sulcus can be determined by the phase reversal of N20.

Giant SSEPs are seen in patients with cortical myoclonus, such as patients with progressive myoclonic epilepsies.

**51. B**

BAEPs are useful for monitoring peripheral and central auditory pathways intraoperatively. In the operating room, sudden loss of the BAEP can occur with ischemia involving the internal auditory nerve.

Wave I on the BAEP corresponds to the peripheral portion of CN 8.

If wave I is absent but the other waves are normal, the patient has peripheral hearing loss.

Brain death may result in loss of all waveforms or loss of all waveforms after wave I. (In 2023, the American Academy of Neurology published an updated guideline on pediatric and adult brain death/death by neurologic criteria, which states that EEG, auditory evoked potentials (AEPs), and somatosensory evoked potentials (SSEPs) should *not* be used as ancillary tests to assist in the diagnosis of brain death.[1])

A vestibular schwannoma can cause a prolonged latency between waves I and III.

Demyelinating disease may result in increased latency between waves III and V. (Wave III corresponds to the superior olivary complex in the pons, and wave V corresponds to the inferior colliculus in the midbrain.) Wave V may be absent in patients with multiple sclerosis.

The BAEP pathway can be remembered by the mnemonic NCSLIMA: cranial *n*erve VIII (wave I) → *c*ochlear nuclei in the medulla (wave II) → *s*uperior olivary complex in the pons (wave III) → *l*ateral lemniscus in the pons (wave IV) → *i*nferior colliculus in the midbrain (wave V) → *m*edial geniculate nucleus in the thalamus (wave VI) → *a*uditory radiations (wave VII).

**52. C**

This is the definition for the ictal-interictal continuum.[2]

Brief potentially ictal rhythmic discharges (BIRDs) last less than 10 seconds. BIRDs are abnormal activity without a definite clinical correlate that is more than 4 Hz. BIRDs have at least one of the following three features: They evolve, they are similar to the patient's interictal discharges or seizures, or they are sharply contoured.[2]

The term CAPE refers to the finding of two patterns lasting at least 10 seconds that alternate for at least six cycles.[2]

WHAM is a pattern of phantom 6-Hz spike and wave discharges. WHAM refers to *w*akefulness, *h*igh-amplitude spike, *a*nterior, and *m*ale. These discharges can also be seen in a FOLD pattern, which stands for *f*emale, *o*ccipital, *l*ow-amplitude spike, and *d*rowsiness. Historically, FOLD has been considered a benign variant, and WHAM has been thought to have a stronger correlation with epilepsy; however, some authors consider both to be of uncertain clinical significance.[3]

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# 23.

# NEUROTOXICOLOGY

## QUESTIONS

1. **A mother brings her 3-year-old child for evaluation because of change in personality and lethargy. The physical examination is remarkable for a line around the gum margins. Laboratory studies show a microcytic anemia. Radiographic studies show opaque bands at the metaphysis of the lower femur and upper tibia. Which of the following is most likely responsible?**
   A. Aluminum toxicity
   B. Arsenic poisoning
   C. Cadmium exposure
   D. Lead toxicity
   E. Mercury poisoning

2. **Which of the following is the most likely presentation of lead toxicity in adults?**
   A. Insomnia
   B. Paresthesias
   C. Tremor
   D. Wrist drop

3. **A 50-year-old woman presents with lower extremity paresthesias. On examination, she has alopecia and palmar and plantar keratosis. There are white lines across her nails. She has decreased ankle reflexes and decreased pinprick, vibration, and proprioception in her feet. Exposure to which of the following best explains her symptoms?**
   A. Arsenic
   B. Bismuth
   C. Magnesium
   D. Mercury
   E. Tin

4. **Which of the following substances causes erethism?**
   A. Arsenic
   B. Cyanide
   C. Ethylene oxide
   D. Mercury
   E. Thallium

5. **Fill in the blank: Alopecia can occur with ____________________ toxicity.**
   A. Copper
   B. Lead
   C. Nickel
   D. Thallium

6. **What is the mechanism of action of botulinum toxin?**
   A. It decreases acetylcholine release.
   B. It blocks the acetylcholine receptor.
   C. It inhibits acetylcholinesterase.
   D. It antagonizes the glycine receptor.
   E. It acts as an agonist at the glutamate receptor.

7. **A 6-year-old presents with vomiting, altered mental status, miosis, bradycardia, and wheezing after visiting a farm. On examination, he is weak and has fasciculations. What is the mechanism of action of the agent to which he was exposed?**
   A. It inactivates acetylcholinesterase.
   B. It prevents release of acetylcholine.
   C. It blocks the acetylcholine receptor.
   D. It antagonizes the glycine receptor.
   E. It acts as an agonist at the glutamate receptor.

8. **Which of the following is found in reef fish, opens the sodium channel, and causes paresthesias and paradoxical sensory disturbances?**
   A. Ciguatoxin
   B. Tetrodotoxin
   C. Saxitoxin
   D. Latrotoxin

9. **Which marine toxin is a glutamate receptor agonist and causes amnestic shellfish poisoning?**
   A. Brevetoxin
   B. Domoic acid
   C. Tetrodotoxin
   D. Mu conotoxin

10. **A 23-year-old man is bitten by a black widow spider. What is the mechanism of action of its venom?**
    A. It acts as an agonist at the glutamate receptor.
    B. It antagonizes the glycine receptor.
    C. It blocks the acetylcholine receptor.
    D. It increases the release of neurotransmitters.
    E. It inhibits acetylcholinesterase.

11. **Exposure to which of the following is *least* likely to affect the basal ganglia?**
    A. Carbon monoxide
    B. Copper
    C. Manganese
    D. Nickel

12. **A 20-year-old ingests *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). What symptoms are expected?**
    A. Parkinsonian symptoms
    B. Schizophrenia symptoms
    C. Miosis and sedation
    D. Superhuman strength

13. **Which of the following chemicals causes retinal ganglion cell degeneration and necrosis of the putamina?**
    A. Acrylamide
    B. Ethylene glycol
    C. Hexane
    D. Methanol
    E. Trichloroethylene

14. **A 20-year-old man presents with unsteady gait and tingling in his legs. He has decreased vibration and position sensation in a stocking-glove distribution. Ankle reflexes are decreased, but patellar reflexes are hyperreactive. Which of the following is the most likely cause?**
    A. Nitrous oxide abuse
    B. Strychnine poisoning
    C. Tetanus
    D. Toluene abuse
    E. Vacor toxicity

15. **A 3-year-old presents with bradycardia, somnolence, and miosis. Which of the following is the most likely cause?**
    A. Clonidine toxicity
    B. Diphenhydramine overdose
    C. 3,4-Methylenedioxy-methamphetamine (MDMA)
    D. Salicylate poisoning

16. **Excessive zinc ingestion can cause a myelopathy due to which of the following?**
    A. Copper deficiency
    B. Magnesium deficiency
    C. Vitamin $B_{12}$ deficiency
    D. Vitamin E deficiency

17. **Which of the following is a treatment for cyanide poisoning?**
    A. Acetylcysteine
    B. Fomepizole
    C. Hydroxocobalamin hydrochloride
    D. Methylene blue
    E. Penicillamine

18. **Which of the following is *least* likely to cause hyperthermia?**
    A. Baclofen withdrawal
    B. γ-Hydroxybutyrate (GHB) ingestion
    C. Salicylate toxicity
    D. Serotonin syndrome

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# NEUROTOXICOLOGY

## ANSWERS

**1. D**

This patient has been exposed to lead. Lead toxicity causes lead lines along the gums and in the long bones. Lead affects porphyrin metabolism. It can cause microcytic anemia, and basophilic stippling of red blood cells may be seen. Lead toxicity can also cause proximal renal tubular dysfunction. Lead encephalopathy caused by inorganic lead (found in paint) is treated with chelation.

Aluminum was associated with dialysis encephalopathy/dialysis dementia. This is less common following changes in dialysis. Aluminum also caused "pot room palsy." Memory problems and incoordination were seen in workers in the pot room of smelting plants. Osteodystrophy and anemia can also be seen in aluminum toxicity.[1]

Cadmium causes flu-like symptoms.

**2. D**

The most common presentation of lead toxicity in adults is wrist drop. Lead causes an asymmetric motor neuropathy involving the wrist and finger extensors.

**3. A**

This patient has chronic arsenic toxicity. It manifests as a sensorimotor peripheral neuropathy. Other characteristic features are Mees lines (white lines across the nails due to growth disruption), hyperkeratosis of the palms and soles, and alopecia.

Acute arsenic poisoning may manifest with an ascending peripheral neuropathy resembling Guillain–Barré syndrome. Gastrointestinal symptoms are severe. Patients have vomiting and "rice water" diarrhea. The patients' breath may have a garlic odor. Chelating agents such as dimercaprol and succimer are used to treat arsenic poisoning.

Bismuth can cause acute renal failure. Chronic exposure can cause a myoclonic encephalopathy similar to Creutzfeldt–Jakob disease. Blue-black gum discoloration is also characteristic of chronic bismuth poisoning.

Tin can be found in the plastic and agriculture industries. Triethyl tin is associated with edema and vacuolar changes in central myelin. Trimethyl tin is associated with seizures.[1]

**4. D**

Exposure to mercury can occur during the production of chemicals, paints, paper, plastics, and fungicides. Mercury can be found in multiple forms.

Inorganic mercury includes elemental mercury vapor and mercury salts. Inhaled mercury vapor primarily affects the brain. Mercury salts tend to affect the gastrointestinal tract and the kidneys. Acute poisoning with inorganic mercury causes delirium. It is associated with respiratory distress, profuse vomiting, metallic breath/taste, bloody diarrhea, and renal failure. Chronic exposure to inorganic mercury causes personality changes, polyneuropathy, and tremor. Gingivitis and renal dysfunction also occur. The personality changes seen with inorganic mercury poisoning are referred to as *erethism*. Initially, shyness and withdrawal are seen. Later, irritability occurs. The term "mad as a hatter" is derived from the personality changes seen in manufacturers of felt hats, who were exposed to mercuric salts. Acrodynia ("pink disease") occurs with chronic inorganic mercury poisoning in children. It is characterized by a painful neuropathy (painful erythematous digits) with autonomic symptoms.

Organic mercury includes compounds in which mercury is bonded to a structure with carbon atoms. Exposure to organic mercury causes cognitive problems, ataxia, constricted visual fields, polyneuropathy, and circumoral and acral paresthesias. Methylmercury, which is a type of organic mercury, is found in certain fish. Minamata disease is caused by methylmercury poisoning; the classic outbreak occurred in humans who consumed fish and shellfish that were contaminated with methylmercury, which had been dumped by a chemical plant into Minamata Bay in Japan.

Ethylene oxide is a gas sterilant. Exposure has been reported in operating room nurses. A rash appears at uncovered areas. Peripheral neuropathy, memory problems, and headaches have also been reported.[2] Symptoms improve on the weekend.[1]

**5. D**

Alopecia can occur with thallium toxicity. Thallium is found in rodenticides and insecticides. It competes with potassium ion transport in the $Na^+/K^+$ adenosine triphosphatase system.

Acutely, thallium can cause altered mental status, vomiting, optic neuropathy, autonomic dysfunction (including hypertension), and a painful ascending neuropathy. With chronic exposure, alopecia and Mees lines are seen. Arsenic can also cause alopecia and Mees lines.

Thallium poisoning is in the differential diagnosis of Guillain–Barré syndrome. Alopecia helps differentiate thallium poisoning. Reflexes are relatively preserved in thallium poisoning, but there may be cranial nerve involvement. Patients with thallium poisoning also have painful joints.

**6. A**

Botulinum toxin is produced by the bacteria *Clostridium botulinum*. The toxin causes decreased acetylcholine release, which results in muscle relaxation.

**7. A**

This patient has organophosphate poisoning. Organophosphates inactivate acetylcholinesterase, resulting in decreased hydrolysis of acetylcholine.

Cholinergic poisoning, such as from organophosphates, causes altered mental status, miosis, lacrimation, rhinorrhea, salivation, diaphoresis, bradycardia, bronchospasm, vomiting, diarrhea, urination, muscle fasciculations, and weakness.

Atropine is an antagonist at muscarinic receptors; it helps prevent increased secretions, bronchoconstriction, and bradycardia in patients with organophosphate poisoning. However, it is not effective against the neuromuscular effects that result from moderate to severe intoxication. Pralidoxime (2-PAM), which is a cholinesterase reactivator, treats weakness due to organophosphate poisoning.

**8. A**

The most common food poisoning illness caused by seafood is ciguatera. Multiple toxins have been found in ciguatera. The most common is ciguatoxin. Ciguatoxin is produced by dinoflagellates found in reef fish such as barracuda, grouper, and snapper. It opens sodium channels, causing depolarization. Vomiting and diarrhea appear within 8 hours after ingestion. Paradoxical sensory disturbances are characteristic (e.g., hot feels cold and vice versa). Fatigue, weakness, and areflexia may be present.

Saxitoxin is a sodium channel blocker. It causes paralytic shellfish poisoning.

Latrotoxin is found in the black widow spider.

**9. B**

Domoic acid, which is an ingestible marine toxin that affects the central nervous system, is produced by a diatom found in shellfish. It is a glutamate receptor agonist that has an affinity for the hippocampus. It can cause headache, acute encephalopathy, permanent memory loss, seizures, and coma. It also produces gastrointestinal symptoms.

Tetrodotoxin is a fatal toxin found in pufferfish. The sodium channels that are responsible for initiation of axonal action potentials are sensitive to tetrodotoxin. Tetrodotoxin, saxitoxin, and mu conotoxin all bind to the sodium voltage-gated ion channels and block sodium influx.

Brevetoxin, which is produced by red tide dinoflagellates in shellfish, opens slow sodium channels along sensory axons. Similar to ciguatoxin, it can cause reversal of hot and cold temperature sensation. It also causes paresthesias and ataxia.

**10. D**

The black widow spider releases latrotoxin. α-Latrotoxin stimulates neuronal calcium channels, causing release of synaptic vesicles. It causes presynaptic facilitation of neurotransmitter release (e.g., acetylcholine, GABA, glutamate). Symptoms include muscle and chest pain, dysarthria, hyperhidrosis, and anxiety.

**11. D**

Carbon monoxide causes bilateral globus pallidus necrosis. Carbon monoxide poisoning can be treated with hyperbaric oxygen.

In Wilson disease, copper accumulates in multiple tissues, including the brain. Patients may have chorea, dystonia, tremor, or parkinsonian symptoms. Magnetic resonance imaging shows increased T2 signal in the basal ganglia and thalamus. The “face of the giant panda” sign may be seen in the midbrain on axial T2-weighted images.

Manganese can cause parkinsonism. Increased T1 signal is seen in the striatum bilaterally, especially the globus pallidus.

Nickel can cause cerebral edema acutely.

**12. A**

MPTP, an analog of meperidine, causes loss of melanin-containing dopaminergic neurons in the substantia nigra, which results in parkinsonian symptoms.

Chronic exposure to carbon disulfide can also cause parkinsonism.

**13. D**

Methanol ingestion can cause hemorrhagic necrosis of the putamina. It also can cause dilated pupils, retinal edema, degeneration of ganglion cells, and blindness.

Methanol can be found in antifreeze, windshield wiper fluid, solvents, and adulterated alcoholic beverages. It causes discoordination, headache, vomiting, and impaired vision. It also produces a metabolic acidosis with a large anion gap and an elevated osmolar gap.

Methanol is metabolized by alcohol dehydrogenase to formaldehyde. Then formaldehyde is converted to formic acid by aldehyde dehydrogenase. Formic acid is a neurotoxin. Fomepizole, which inhibits alcohol dehydrogenase, has been used as an antidote to methanol poisoning. Ethanol, which competes with the metabolism of methanol, has also been used to treat methanol toxicity. Bicarbonate may be required to treat the metabolic acidosis.

Ethylene glycol is in antifreeze. Ingestion of ethylene glycol causes organic acidosis, coma, and renal failure. Like methanol, ethylene glycol can cause metabolic acidosis with an increased anion gap. Patients with isopropyl alcohol

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poisoning, on the other hand, have ketones and an osmol gap without metabolic acidosis. They also tend to have fruity-smelling breath.[3]

Thallium and trichloroethylene can cause cranial neuropathies. Toxicity from trichloroethylene can cause trigeminal neuropathy.

Thallium, acrylamide, and *n*-hexane cause neuropathy with prominent autonomic dysfunction.[1]

Acrylamide exposure occurs in the plastic industry. It causes an axonal neuropathy. Redness and skin exfoliation can be seen. There is significant improvement when exposure ends.[1]

Hexane causes a peripheral neuropathy. Axonal swellings are characteristic. Automotive technicians may be exposed to hexane. Glue sniffing and gasoline sniffing may also result in hexane toxicity. Symptoms can progress for a time even after the exposure ends.[1]

**14. A**

This patient's examination findings are consistent with nitrous oxide abuse, which can produce a myelopathy resembling that caused by vitamin $B_{12}$ deficiency. A proposed mechanism is that nitrous oxide inhibits methionine synthase, which converts homocysteine to methionine. Vitamin $B_{12}$ is a cofactor in this reaction.

Strychnine is found in rat poisoning. It can cause painful muscle spasms, seizures, and rhabdomyolysis. Tetanospasmin, which causes tetanus, and latrotoxin from the black widow spider can also cause severe muscle spasms. Although opisthotonos and risus sardonicus are classic signs of tetanus, they can also occur with strychnine poisoning. Benzodiazepines are helpful in the treatment of muscle spasms caused by strychnine, tetanospasmin, or latrotoxin.

Toluene is found in certain glues and paints. Acutely, it can cause headache, unsteadiness, hallucinations, tremors, seizures, and coma. It can also cause vomiting, respiratory depression, renal tubular acidosis, and chemical pneumonitis. Chronically, it can cause leukoencephalopathy. It can cause tremor, ataxia, cerebellar atrophy, and an abnormal brainstem auditory evoked response.

Vacor, which is also known as *N*-3-pyridylmethyl-*N′*-*p*-nitrophenyl urea (PNU), is a phenylnitrosourea that was in rodent poison. It antagonizes nicotinamide metabolism.[4] Vacor can cause acute quadriparesis. It causes an axonal neuropathy. Cranial nerve abnormalities, autonomic dysfunction, and diabetes mellitus may also be present.[5] Pancreatitis causes hyperglycemia.[2] Niacinamide has been used for treatment of vacor toxicity.[5]

**15. A**

Clonidine can cause sedation, bradycardia, respiratory depression, and miosis. It resembles opiate toxicity but is only partially responsive to naloxone. Opiates cause sedation, miosis, and respiratory depression. They can cause flash pulmonary edema. Other causes of miosis are barbiturates, cholinergics, organophosphates, phenothiazines, and ethanol. Phencyclidine (PCP) can cause miosis or mydriasis. Nystagmus may be present in patients with PCP intoxication as well.

MDMA, which is known as Ecstasy, is a derivative of methamphetamine. It also has some structural similarities to the hallucinogen mescaline, which is found in peyote.

MDMA causes a sympathomimetic syndrome, similar to that caused by amphetamines, methamphetamine, cocaine, crack, epinephrine, ephedra (in dietary supplements), ephedrine, pseudoephedrine, and monoamine oxidase inhibitors (MAOIs). It causes agitation, pressured speech, mydriasis, tachycardia, hypertension, hyperthermia, hyperreflexia, rhabdomyolysis, and tremor. β-Blockers should be avoided to prevent unopposed alpha-induced vasoconstriction.

MDMA acts primarily at the serotonin transporter (SERT). In addition to increasing serotonin levels, it increases dopamine and norepinephrine levels. Because MDMA affects serotonin, it can contribute to serotonin syndrome.

Serotonin syndrome causes agitation, mydriasis, hyperthermia, tachycardia, diaphoresis, vomiting, diarrhea, shivering, hyperreflexia, clonus (including ocular), and myoclonus. Many medications can contribute to serotonin syndrome, including selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), stimulants, lithium, tramadol, dextromethorphan, meperidine, fentanyl, triptans, linezolid, St. John's wort, and tryptophan. Cyproheptadine is used in the treatment of serotonin syndrome.

Neuroleptic malignant syndrome (NMS) and serotonin syndrome have similarities. Both cause fever, altered mental status, and autonomic dysfunction. Therefore, antipsychotics should be avoided in suspected serotonin syndrome, in case the patient actually has NMS. NMS tends to have longer onset than serotonin syndrome. Bradykinesia is more consistent with NMS, whereas hyperreflexia, clonus, myoclonus, and shivering are more consistent with serotonin syndrome (see Table 23.1).

*Table 23.1* NEUROTOXICOLOGY SYNDROMES

| SYNDROME | DISTINGUISHING FEATURES |
|---|---|
| **Anticholinergic syndrome** | **Dry, flushed skin and absent bowel sounds** |
| **Sympathetic syndrome** | **Diaphoresis and normal bowel sounds** |
| **Serotonin syndrome** | **Hyperreflexia, clonus, myoclonus, and shivering** |
| **Neuroleptic malignant syndrome** | **Rigidity and bradykinesia** |

In addition to hyperthermia, mental status changes, and autonomic instability, NMS causes rigidity and leukocytosis. Rhabdomyolysis can occur, resulting in elevated creatine phosphokinase levels. Liver function enzyme levels are high, and iron is low. NMS that is caused by an antipsychotic usually occurs within the first 2 weeks of treatment. It can also occur when a patient who is taking a dopaminergic medication abruptly discontinues it.

NMS is treated with supportive care. Fluid resuscitation is important to protect kidney function, and alkalinization of the urine may be necessary. Benzodiazepines, dopamine agonists, and dantrolene have been used for treatment.

In addition to NMS, antipsychotics can cause dystonic reactions, extrapyramidal side effects, anticholinergic side effects, and orthostatic hypotension. Some have serotonergic effects as well.

Anticholinergic medications, such as diphenhydramine and TCAs, also cause confusion, tachycardia, and hyperthermia, but bowel sounds are absent in anticholinergic poisoning and present in sympathomimetic poisoning. In addition, anticholinergic poisoning causes dry, flushed skin, whereas sympathomimetics cause diaphoresis. Diphenhydramine can also cause seizures.

**16. A**

Excessive zinc ingestion may lead to reduced intestinal absorption of copper. This may result in copper deficiency, which can cause myelopathy. Zinc can be found in cold medicines and dental adhesives.

Copper deficiency can also occur with malabsorption—for instance, after bariatric surgery.

Myelopathy due to copper deficiency resembles subacute combined degeneration due to vitamin $B_{12}$ deficiency. Patients have decreased vibration and joint position sensation, paresthesias, sensory ataxia, spasticity, brisk deep tendon reflexes, and extensor plantar responses.

**17. C**

Hydroxocobalamin hydrochloride is used to treat cyanide toxicity. In addition to intentional poisoning or exposure during manufacturing, cyanide toxicity can occur with smoke inhalation. Cyanide interacts with cytochrome oxidase. It causes cardiovascular collapse and coma. Classically, cyanide has been associated with a "bitter almond" odor, but this may not be present. Patients have evidence of hypoxia but may not be cyanotic until later. The skin initially may be flushed. Lactic acidosis is also a clue.

Acetylcysteine is used to treat acetaminophen poisoning.

Fomepizole is used to treat methanol and ethylene glycol poisoning. Ethanol is also used to treat these conditions.

Methylene blue is the treatment for methemoglobinemia. Multiple medications can cause methemoglobinemia. One is benzocaine, which is found in some forms of Orajel.

Penicillamine is used to treat lead, mercury, and copper poisoning (see Table 23.2).

*Table 23.2* TREATMENTS FOR SPECIFIC POISONS

| MEDICATION | CONDITION TREATED |
|---|---|
| **Fomepizole** | **Methanol and ethylene glycol poisoning** |
| **Hydroxocobalamin hydrochloride** | **Cyanide toxicity** |
| **Methylene blue** | **Methemoglobinemia** |
| **Penicillamine** | **Lead, mercury, and copper poisoning** |

**18. B**

Anticholinergic syndrome, baclofen withdrawal, salicylate toxicity, serotonin syndrome, and neuroleptic malignant syndrome can cause hyperthermia.

Gamma-hydroxybutyrate (GHB) is used to treat narcolepsy. It reduces daytime sleepiness and cataplexy. It can also cause amnesia, leading to its abuse. GHB *withdrawal* can cause hyperthermia. GHB *intoxication* can cause hypothermia. GHB intoxication also causes central nervous system and respiratory depression, myoclonic jerks and seizure-like activity, vomiting, and bradycardia. Patients may recover suddenly several hours after ingestion.

Salicylate poisoning first results in hyperventilation and respiratory alkalosis. This is followed by metabolic acidosis with an increased anion gap. Patients can have hyperthermia, vomiting, seizures, coma, and cardiovascular collapse.

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# 24.

# PAIN AND HEADACHE

## QUESTIONS

1. **A 34-year-old woman with no significant past medical history presents to the clinic with six episodes of throbbing headaches. The headaches are located at her left temple and are associated with light sensitivity, sound sensitivity, and occasional nausea. The headaches can last 4 hours to 3 days. What is her diagnosis?**
   A. Cluster headache
   B. Chronic migraine with aura
   C. Migraine without aura
   D. Hemicrania continua

2. **Which medication would be an appropriate migraine treatment for the patient from Question 1? She notes that she is in the process of trying to get pregnant with her partner.**
   A. Topiramate
   B. Valproic acid
   C. Calcitonin gene-related peptide (CGRP) inhibitor
   D. Acetaminophen and fluid hydration

3. **A 45-year-old man presents to your clinic with a 3-month history of stabbing pain over his right eye that occurs up to seven times daily. The pain is associated with conjunctival injection and lacrimation that usually lasts approximately 40 minutes. What is the most likely diagnosis?**
   A. Cluster headache
   B. Migraine without aura
   C. Paroxysmal hemicrania
   D. Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)

4. **A 50-year-old man with a past medical history of hypertension, diabetes, and stroke presents to your office with a 1-year history of constant left-sided headache. The headache starts at his temple, radiates to the back of his head, and lasts all day. The headache is associated with left eyelid swelling and a sense of restlessness. Rest does not make it better, and it returns upon waking. It is not associated with photophobia, phonophobia, nausea, or dizziness. He has tried acetaminophen, caffeine, ibuprofen, topiramate, and valproic acid, all without relief. Which medication should be prescribed?**
   A. Sumatriptan
   B. CGRP receptor inhibitor
   C. Indomethacin
   D. Botox

5. **A 40-year-old woman with a past medical history of migraine presents to the clinic with a 4-month history of new headaches. She describes a stabbing pain over the right side of her head located over her eye and in the temple. The stabbing pain happens at least five times a day and lasts between 5 and 10 minutes. When the pain starts, it causes her right eye to run and get red. What is the most likely diagnosis?**
   A. Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)
   B. Paroxysmal hemicrania
   C. Primary stabbing headache
   D. Short-lasting unilateral neuralgiform headache with autonomic symptoms (SUNA)

6. **A 60-year-old man with a history of hypertension, multiple cysts on his kidneys, and heart failure requiring an automated implantable cardioverter defibrillator presents to the emergency department due to an acute headache that he describes as the worst headache of his life. It is a holocephalic headache that is associated with nausea, vomiting, photophobia, and neck stiffness. A computed tomography (CT) scan of the head appears to be within normal limits. What is the next step in management?**
   A. Magnetic resonance imaging (MRI) of the brain
   B. Lumbar puncture
   C. Discharge home
   D. Neurosurgery consultation

7. **An 18-year-old woman with a past medical history of obesity and polycystic ovary syndrome, who is on birth control, reports daily throbbing headache for 6 months that is located at the right temple. She endorses increased pressure when she coughs or leans forward. MRI of the brain is negative for any intracranial masses or lesion. What other sign/symptom might she have?**
   A. Cranial nerve IV palsy
   B. Rhinorrhea
   C. Ptosis
   D. Tinnitus

8. **A 30-year-old woman undergoes epidural anesthesia for the birth of her child. Five hours later, she notes a severe holocephalic headache when she sits up to nurse her child. The headache persists for 2 days and is associated with nausea. MRI demonstrates pachymeningeal enhancement. What is the best treatment for her headache?**

A. Sumatriptan
B. Caffeine
C. Blood patch
D. Topiramate

**9. An 8-year-old girl has been to the doctor multiple times with her parents due to frequent episodes of severe abdominal pain. The pain is periumbilical and is associated with nausea, vomiting, photophobia, and anorexia. She has had a total of six episodes separated by 3 or 4 weeks. She has missed more than 1 month of school. She has seen a gastroenterologist, who has not found anything abnormal on any of her examinations or diagnostic studies. What is the most likely diagnosis?**

A. Migraine with aura
B. Cyclical vomiting
C. Factitious disorder
D. Abdominal migraine

**10. A 38-year-old woman has been training for a marathon; after running 10 miles, she experiences a diffuse throbbing pain in her head. It is nonradiating and lasts for 5 hours. It starts to ease in intensity after she drinks water and lays down. The next week she continues her training and runs another 12 miles. She experiences the same type of headache, this time lasting 1 full day. Before diagnosing her with primary exercise headache, what studies should be done?**

A. Lumbar puncture
B. CT angiogram of the head and neck
C. MRI of the brain without contrast
D. MR venogram

**11. A 75-year-old woman with a past medical history of hypertension and arthritis presents to your clinic due to 2 weeks of right temporal headache associated with jaw pain, fever, 5-pound weight loss, and anemia. What is the best method for establishing the diagnosis?**

A. MRI brain without contrast
B. Fundoscopy
C. CT angiogram of the head and neck
D. Temporal artery biopsy

**12. A 12-year-old-boy with no past medical history presents to the clinic with his mother due to severe headaches that have been getting worse during the past month. The patient wakes up due to diffuse head pain. He has been nauseated; endorses photophobia; and has worsening pain when he coughs, sneezes, or leans forward. What is the next step in management?**

A. Start ondansetron and advise the patient to keep a headache diary
B. Acetaminophen and fluid hydration
C. MRI brain
D. Lumbar puncture

**13. A 45-year-old man presents to the emergency department due to severe acute-onset headache that has occurred three times in the past 2 weeks. The patient describes the pain as sudden and severe. It usually occurs after he has done some form of physical activity. The patient endorses diffuse pain that reaches peak intensity within 1 minute and is associated with photophobia and nausea. Lumbar puncture is normal. What is the classic radiographic finding you expect to see?**

A. Subarachnoid blood on CT
B. Moyamoya
C. Meningeal enhancement on MRI
D. String of beads appearance on angiography

**14. A 68-year-old man with a history of chronic uncontrolled diabetes presents to your clinic with painful burning sensation in both feet up to his mid shins and in both hands up to his wrists. What type of nerve fibers are affected?**

A. Aα and C
B. C and Aδ
C. Aβ and Aδ
D. Aα and Aβ

**15. Which of the following is more typical of migraine without aura than of migraine with aura?**

A. Visual changes
B. Increased risk of ischemia
C. Cortical spreading depression
D. A relationship to the menstrual cycle

**16. Which of the following medications does *not* act on the $\alpha_2\delta$ subunit of the N-type calcium channel?**

A. Capsaicin
B. Gabapentin
C. Pregabalin
D. Topical lidocaine

**17. A 30-year-old woman presents to the office due to persistent burning pain, weakness, and swelling in her left hand after suffering a left radius fracture. The burning sensation is severe and is exacerbated with movement of the hand. She also reports more hair growth over the dorsum of the left hand and decreased sweating. What is the most likely diagnosis?**

A. Dejerine–Roussy syndrome
B. Complex regional pain syndrome (CRPS)
C. Poor casting
D. Radicular pain

**18. Which of the following is *not* a mechanism of action of topiramate?**

A. Blockage of voltage-gated sodium channels
B. Increased γ-aminobutyric acid (GABA) activity
C. Carbonic anhydrase inhibitor
D. Agonist at the 5-$HT_{1F}$ receptor

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**19. A 65-year-old man with a history of coronary artery disease, hypertension, and migraine with aura presents to your office for advice on abortive therapy. Which of the following treatments would be the best option for him?**

A. Sumatriptan
B. Ubrogepant
C. Dihydroergotamines (DHEs)
D. High-dose ibuprofen

**20. What is the mechanism of action of lasmiditan?**

A. $5\text{-HT}_{1B/1D}$ receptor antagonist
B. $5\text{-HT}_{1F}$ agonist
C. Monoclonal antibody against CGRP
D. CGRP receptor antagonist

**21. A 40-year-old woman with a history of chronic migraine presents to the emergency department with a 4-day history of severe left-sided headache associated with photophobia, phonophobia, nausea, vomiting, and soreness of her left temple. She has been taking topiramate regularly but ran out of sumatriptan 4 days prior to presentation. Which of the following would be most beneficial to the patient?**

A. Prescribe more sumatriptan.
B. Order a stat MRI of her brain.
C. Initiate a new preventative therapy because topiramate is no longer effective.
D. Administer intravenous DHE.

**22. Which of the following is *not* involved in migraine pathophysiology?**

A. Nitric oxide
D. 5-Hydroxytryptamine
C. CGRP
D. Interleukin-1

**23. What is the mechanism of action of the "Gepant" drugs that are used for management of migraine?**

A. Monoclonal antibody against CGRP or its receptor
B. CGRP receptor antagonist
C. $5\text{-HT}_{1A}$ receptor agonist
D. $5\text{-HT}_{1B/1D}$ receptor agonist

**24. An 8-year-old child with intractable epilepsy is found to have a sodium channel mutation. His mother has a history of severe migraines with episodes of hemiplegia that can last up to 24 hours. Which condition is most likely to be associated with his epilepsy type?**

A. Migraine with basilar aura
B. Familial hemiplegic migraine (FHM) type 1
C. Familial hemiplegic migraine type 2
D. Familial hemiplegic migraine type 3

**25. A 25-year-old man accidentally overdoses on opiates that he finds in his grandfather's medicine cabinet. He falls asleep on the floor for 12 hours and wakes up with severe burning pain in his left thigh. Which term describes the pain he is experiencing?**

A. Allodynia
B. Hyperpathia
C. Radiculopathy
D. Causalgia

**26. What is the mechanism of action of sumatriptan?**

A. It is a $5\text{-HT}_{1A}$ receptor antagonist.
B. It is a $5\text{-HT}_{1B/1D}$ receptor agonist.
C. It is a $5\text{-HT}_{2A/2C}$ receptor antagonist.
D. It is a $5\text{-HT}_{3}$ agonist.

**27. A 30-year-old patient with a previous diagnosis of migraines presents with a complaint of daily headaches for the past 3 months. Unlike her migraines, these headaches are not associated with photophobia or vomiting. She says the headaches are constant, so she must take ibuprofen at least twice daily. Her examination findings are normal. Which of the following topics needs to be discussed with this patient?**

A. The benefits of naproxen over ibuprofen
B. The benefits of alternating ibuprofen and acetaminophen
C. The benefits of indomethacin over ibuprofen
D. Medication-overuse headache

**28. A 45-year-old man presents with recurrent headaches when he coughs. He has sudden, bilateral head pain when he coughs, lasting for a few seconds. He does not have any other types of headaches or triggers. What is the most effective treatment?**

A. Antitussives
B. Indomethacin
C. Naproxen
D. Verapamil

**29. Match each term with its definition.**

1) Allodynia
2) Hyperalgesia
3) Hyperpathia
4) Dysesthesia
5) Causalgia

A. Delayed, increased pain from a noxious stimulus
B. Pain from a non-noxious stimulus
C. Pain from a noxious stimulus that is significantly greater than expected
D. Unpleasant sensation (spontaneous or provoked)
E. A burning pain occurring after peripheral nerve injury

**30. Which of the following is the gold standard for diagnosis of small-fiber neuropathy?**

A. Electromyography (EMG)
B. Nerve conduction studies (NCSs)
C. Skin biopsy
D. Sural nerve biopsy

**31. Which of the following is part of the spinothalamic system?**

A. Bare nerve endings
B. Golgi tendon organs
C. Meissner's corpuscles
D. Pacinian corpuscles

**32. Which of the following neuropeptides/neurotransmitters is most specific to pain pathways involving C fibers?**

A. Adenosine
B. Substance P
C. Neuropeptide Y
D. Neurotensin

**33. Mutations in which of the following channels can cause increased pain sensitivity? (Other mutations in this channel can cause congenital inability to experience pain.)**

A. Chloride
B. Potassium
C. Sodium
D. Magnesium

**34. Which of the following conditions may be followed by migraine variants and eventually by migraine with aura when the patient is older? (Some cases of this condition have been linked to mutations in *CACNA1A*.)**

A. Benign paroxysmal torticollis of infancy
B. Episodic ataxia 1
C. Paroxysmal kinesigenic dyskinesia
D. Paroxysmal tonic upgaze of infancy

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# PAIN AND HEADACHE

## ANSWERS

**1. C**

Migraine is a primary headache disorder. To be diagnosed with migraine without aura, a patient must have experienced at least five attacks. The attacks must last 4–72 hours and meet at least two of the following criteria: unilateral location, pulsatile in quality, moderate to severe intensity, and aggravated by routine physical activity (or activity is avoided). The patient must have associated nausea and/or vomiting or photophobia and phonophobia.[1]

**2. D**

In a patient who is trying to conceive, it is important to consider the risks and side effects of all medications. Topiramate is a category D medication per the U.S. Food and Drug Administration. A child born to a woman who was using topiramate during pregnancy has a higher risk of having a cleft lip and/or palate. Valproic acid also carries the risk of neural tube defects in a child of a mother using this medication during pregnancy. There have not been enough studies to determine if CGRP inhibitors are safe in pregnancy or not, so it is recommended that they not be used during pregnancy. The combination of acetaminophen and fluid hydration is the safest of these options for migraine management in a patient who is pregnant or trying to become pregnant.[2]

**3. A**

The patient is experiencing cluster headaches. Cluster headaches are the most common of the trigeminal autonomic cephalgia (TAC) category of headaches. They occur more often in men. Cluster headaches are associated with severe, unilateral pain that involves the orbital, supraorbital, or temporal regions or a combination of those sites. To be considered a cluster headache, the patient should have experienced at least five attacks. The pain lasts between 15 and 180 minutes and can have a frequency range of once every other day up to eight times a day. The patient must experience at least one of the following associated symptoms with the pain: conjunctival injection and/or lacrimation, nasal congestion and/or rhinorrhea, eyelid edema, forehead and/or facial sweating, miosis and/or ptosis, and agitation/restlessness. During attacks, there is activation in the posterior hypothalamic gray matter region.[1] Oxygen via non-rebreather mask is the treatment for severe cluster headaches. Triggers for cluster headaches include alcohol, histamine, and nitroglycerin.[1]

Paroxysmal hemicrania is also part of the TAC group of headache disorders. To be diagnosed with paroxysmal hemicrania, a patient would have experienced at least 20 attacks of severe unilateral headache involving the orbital or supraorbital region and/or the temple. The patient would experience a feeling of restlessness/agitation or at least one of the following symptoms/signs ipsilateral to the headache: conjunctival injection and/or lacrimation, nasal congestion and/or rhinorrhea, eyelid edema, forehead and facial sweating, or miosis and/or ptosis. The attacks last between 2 and 30 minutes, with a frequency of at least five per day.[1] Paroxysmal hemicrania is treated with indomethacin.[3]

(SUNCT and SUNA are discussed below.)

**4. C**

This patient is experiencing hemicrania continua. Hemicrania continua also falls under the category of TACs. Hemicrania continua is a strictly unilateral, persistent headache. To be diagnosed as having this condition, three criteria must be met. First, the headaches have been present for more than 3 months with intermittent exacerbations. Second, at least one of the following associated symptoms occurs ipsilateral to the pain: conjunctival injection and/or lacrimation, nasal congestion and/or rhinorrhea, eyelid edema, forehead and/or facial sweating, or miosis and/or ptosis. Alternatively, the patient has a sense of agitation or restlessness, or the pain is aggravated by movement. Third, the headache is treated completely by indomethacin.[1]

Sumatriptan, CGRP inhibitors, and botulinum toxin do not relieve hemicrania continua.[3] (See Table 24.1.)

*Table 24.1* **SELECTED TREATMENTS FOR TRIGEMINAL AUTONOMIC CEPHALGIAS**

| DIAGNOSIS | TREATMENT |
|---|---|
| **Cluster headache** | **Oxygen by nonrebreather, sumatriptan** |
| **Hemicrania continua** | **Indomethacin** |
| **Paroxysmal hemicrania** | **Indomethacin** |
| **SUNA/SUNCT** | **Lamotrigine** |

SUNA, short-lasting unilateral neuralgiform headache attacks with cranial autonomic features; SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.

**5. A**

This patient is experiencing short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT). SUNCT is a part of the TAC group of headache syndromes. These types of headaches are unilateral. To meet the diagnostic criteria for SUNCT, patients must have experienced at least 20 attacks with a frequency of at least one a day. The patient feels a brief stabbing pain located in the orbital, supraorbital, temporal, and/or any other trigeminal distribution. The pain can last between 1 and 600 seconds (10 minutes). At least one of the following symptoms accompanies the attacks: conjunctival injection and/or lacrimation, nasal congestion and/or rhinorrhea, eyelid edema, forehead and/or facial sweating, miosis and/or ptosis, or a sensation of fullness in the ear. A lesion in the posterior fossa can cause similar findings to those seen in SUNCT.[1] (See Tables 24.2 and 24.3.)

*Table 24.2* DURATION OF HEADACHES IN TRIGEMINAL AUTONOMIC CEPHALGIAS

| | SUNA/SUNCT | PAROXYSMAL HEMICRANIA | CLUSTER HEADACHE |
|---|---|---|---|
| Duration | 1–600 seconds | 2–30 minutes | 15–180 minutes |

SUNA, short-lasting unilateral neuralgiform headache attacks with cranial autonomic features; SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.

*Table 24.3* FREQUENCY OF HEADACHES IN TRIGEMINAL AUTONOMIC CEPHALGIAS

| | SUNA/SUNCT | PAROXYSMAL HEMICRANIA | CLUSTER HEADACHE |
|---|---|---|---|
| Frequency | At least one per day | At least five per day | One every other day, up to eight per day |

SUNA, short-lasting unilateral neuralgiform headache attacks with cranial autonomic features; SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.

SUNA, which stands for short-lasting unilateral neuralgiform headache with autonomic symptoms, has a similar presentation and similar diagnostic criteria as SUNCT; however, SUNA has less or absent conjunctival injection and lacrimation. SUNA is also a part of the TAC group of headache syndromes. SUNA can resemble trigeminal neuralgia. Trigeminal neuralgia typically has a refractory period after an attack, but SUNA does not.[1]

**6. B**

This patient is likely suffering from a subarachnoid hemorrhage (SAH) in the setting of an aneurysm rupture, given his history of polycystic kidney disease. If there is a high clinical suspicion for a SAH but the CT of the head is not definitive, a lumbar puncture is the next best diagnostic tool. Two elements of the cerebrospinal fluid (CSF) that raise concern for SAH are red blood cells and xanthochromia. Obtaining cardiology clearance for an MRI could take longer than getting the lumbar puncture. This patient should not be discharged home if there is a high clinical suspicion for a SAH. Neurosurgery should be consulted if the lumbar puncture confirms SAH.[4]

**7. D**

This patient has suspected idiopathic intracranial hypertension (IIH). Common symptoms seen in this syndrome include headache, blurred vision, decreased visual fields, tinnitus, increased pressure in the head with bending forward and with Valsalva, diplopia, and abnormalities of cranial nerve VI. Abnormalities of cranial nerves IV and III are not typical in IIH. Rhinorrhea is not typical of this condition but can be seen in TACs.[5]

**8. C**

The patient is experiencing intracranial hypotension secondary to a post-dural puncture headache with a CSF leak. The patient has an orthostatic headache when she moves from a supine position to an upright position. Other symptoms that are common in this condition include nausea, vomiting, visual changes, and change in taste and sensation. The first-line treatment is a blood patch. Caffeine has been used to aid with some of the symptoms but will not treat the CSF leak. Sumatriptan and topiramate are not used to treat post-dural puncture headache. Diffuse pachymeningeal enhancement is seen on MRI with intracranial hypotension. Patients with connective tissue disorders such as Marfan syndrome and Ehlers–Danlos syndrome are at risk for spontaneous intracranial hypotension.[6,7]

**9. D**

This patient is experiencing an abdominal migraine. Abdominal migraine is a type of migraine that presents with abdominal pain that is usually periumbilical, midline, or difficult to localize. The pain can last from 2 to 72 hours and is associated with symptoms such as nausea, vomiting, pallor, or anorexia.[1] There is usually no associated headache, which makes it different than most other migraine types. This condition predominantly affects children and is most commonly found in children younger than age 10 years. Some of these children will go on to develop typical migraine.[1]

Cyclical vomiting is a condition that causes severe, recurring episodes of vomiting without an apparent cause. This is most common in children between ages 3 and 7 years.[8]

**10. B**

The patient is experiencing a primary exercise headache. These headaches occur during or after strenuous activity.

They typically last less than 48 hours.[1] The symptoms seen in primary exercise headache are similar to those of reversible cerebral vasoconstriction syndrome (RCVS) and carotid artery dissection. Therefore, to rule out RCVS and arterial dissection, it is important to obtain a CT angiogram of the head and neck.[9] Indomethacin and β-blockers are used to treat the pain caused by primary exercise headache. Rest and hydration are mainstays in the management of this condition as well. Lumbar puncture would not be a beneficial study in this patient. MRI of the brain without contrast is unlikely to show any intracranial changes. A cerebral venous thrombosis headache usually does not occur during or after exercise specifically; therefore, MR venogram is not the preferred test.

**11. D**

This patient has symptoms consistent with giant cell arteritis (GCA). GCA is caused by the inflammation of large and medium-sized blood vessels. It can commonly affect the aorta, ophthalmic artery, and extracranial branches of the carotid artery.

To make the diagnosis of GCA, according to the American College of Rheumatology original criteria, the patient must fulfill three or more of the following: age 50 years or older, new-onset headache, temporal artery abnormality such as tenderness to palpation or decreased pulsation, elevated erythrocyte sedimentation rate of ≥50 mm/hr, and/or an abnormal temporal artery biopsy.[10] In the 2022 criteria, age 50 years or older is an absolute requirement for the diagnosis of GCA, and a scoring system is provided to aid in diagnosis of the condition. A score of at least 6 points is needed for diagnosis of GCA. A positive temporal artery biopsy or temporal artery "halo sign" on ultrasound is worth 5 points.[11]

In a patient with a high clinical suspicion for GCA, steroids should be initiated immediately. A major complication of this condition is vision loss. The early initiation of steroids can spare vision loss.[4,12]

**12. C**

This patient's symptoms are concerning for increased intracranial pressure. Worsening headaches that occur upon waking and that are accompanied by nausea and vomiting can indicate increased intracranial pressure. Headaches that worsen with coughing, sneezing, Valsalva, or bending forward are also concerning for a process causing increased intracranial pressure such as a tumor. To rule out an intracranial process, it is important to do a thorough neurologic exam including fundoscopy. However, fundoscopy is not always abnormal in a patient with a brain tumor. The next step would be to obtain an MRI of the patient's brain. Starting antiemetics, acetaminophen, and fluids can help the symptoms but will not establish the etiology of the increased intracranial pressure. A lumbar puncture could be dangerous in a patient with increased intracranial pressure and could potentially result in herniation; therefore, brain imaging should be done first.[5]

**13. D**

This patient is experiencing reversible cerebral vasoconstriction syndrome (RCVS). The clinical features of RCVS include a thunderclap headache that reaches peak intensity within 1 minute or severe recurrent headaches, cerebral vasoconstriction in at least two different arteries, and resolution of the vasoconstriction by 3 months.[13] RCVS is associated with pregnancy and puerperium; medications such as selective serotonin reuptake inhibitors, triptans, pseudoephedrine, tacrolimus, and cyclophosphamide; and exposure to drugs such as cocaine, cannabis, amphetamines, and Ecstasy.[13] The imaging findings of RCVS can resemble those of primary angiitis of the central nervous system.[1,14]

**14. B**

Neuropathic pain typically involves C and Aδ nerve fibers, which are small fibers. Small-fiber neuropathies can be painful and length-dependent. The pain usually occurs in a stocking–glove distribution, with exceptions. They can affect temperature sensation and autonomic functions such as sweating. Given this patient's history, it is likely that he is suffering from a small-fiber neuropathy associated with his chronic, uncontrolled diabetes.

Large-fiber neuropathies can cause loss of joint position, sensory ataxia, and loss of vibration sensation.

**15. D**

Migraine without aura often has a relationship to the menstrual cycle. Frovatriptan has been shown to be effective in acute management of menstrual migraine.[2]

Nitric oxide, 5-hydroxytryptyamine (5-HT), and CGRP are all involved in the pathophysiology of migraine with aura.[15] Cortical spreading depression is more often seen in migraine with aura.[1] The trigeminovascular system is involved in mediating the pain experienced in migraine with and without aura. Visual changes such as scintillations, oscillopsia, blind spots, scintillation scotomas, and kaleidoscopic vision are examples of visual auras that occur in patients who experience migraine with aura. Patients who experience migraine with aura have an increased risk of stroke.[4] Smoking cessation is recommended in women who have migraine with aura. Hormone-eluting contraception, especially those higher in estrogen, should generally be avoided in women who experience migraine with aura.

**16. A**

Capsaicin is an agonist at a vanilloid receptor (TPRV1). It causes release of substance P and CGRP.

Gabapentin, pregabalin, and topical lidocaine act on the $\alpha_2\delta$ subunit of the N-type calcium channels.

**17. B**

The patient is suffering from complex regional pain syndrome (CRPS). CRPS is characterized by autonomic changes, sensory abnormalities, motor abnormalities, and trophic changes. CRPS is divided into two types. Type I is known as reflex sympathetic dystrophy, which occurs most often after minor injury to a limb and is less commonly caused by an abnormality of the central nervous system. Type II (causalgia) occurs after injury to a peripheral nerve that results in focal deficits.[16]

Physical therapy, occupational therapy, and psychological treatment are recommended for treatment of CRPS. Medications used to treat CRPS include antiseizure medications such as gabapentin, pregabalin, and carbamazepine; antidepressants; calcium-regulating medications; and corticosteroids. In some cases, sympatholytic procedures are performed.

Dejerine–Roussy syndrome is a central pain syndrome caused by injury to the thalamus, usually the ventroposterolateral nucleus. This thalamic syndrome is characterized by pain on the contralateral side of the body with anesthesia to pinprick. The pain associated with this syndrome can be burning, stabbing, and sharp in quality.

Radicular pain is caused by injury to a peripheral nerve root as it exits the spinal cord. It results in pain and/or numbness and weakness in the dermatome and/or muscle group supplied by that nerve. An extramedullary tumor can cause radicular pain, for example.

**18. D**

Topiramate has multiple mechanisms of action. It blocks voltage-gated sodium channels, it increases GABA activity through a nonbenzodiazepine site on the $\text{GABA}_A$ receptors, it is an α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA)/kainate glutamate receptor antagonist, and it is a carbonic anhydrase inhibitor.[17]

**19. B**

Given the history of coronary artery disease, hypertension, and migraine with aura, this patient should not be prescribed any triptan medications, including sumatriptan. Triptans are contraindicated in patients with a history of ischemic coronary artery diseases, stroke, and transient ischemic attack. Triptans can result in vasospasm, which can exacerbate these conditions. DHE should also be avoided for the same reasons. Ibuprofen can increase blood pressure, so high-dose ibuprofen is not recommended for this patient. The Gepant category of drugs are newer medications that can offer acute migraine management without vasoconstriction and thus are safer for patients with a history of coronary artery disease and stroke/transient ischemic attack.[18]

**20. B**

Lasmiditan is used for the acute treatment of migraine. It is an agonist at $5\text{-HT}_{1F}$ receptors, which are found in the trigeminal ganglion. Lasmiditan is lipophilic and can cross the blood–brain barrier.[19]

**21. D**

This patient is experiencing status migrainosus. Status migrainosus can occur in a person who already experiences migraine with or without aura. The pain is unremitting for more than 72 hours and is debilitating. This patient needs more aggressive treatment than just a change in preventative therapy or administration of a triptan to break this migraine.[17,20] The pain that she is experiencing at the left temple represents cutaneous allodynia. Starting intravenous DHE would be a good option for acute management. DHE is an agonist at $5\text{-HT}_{1B}$, $5\text{-HT}_{1D}$, and $5\text{-HT}_{1F}$ receptors. It also binds to $5\text{-HT}_{1A}$, $5\text{-HT}_{2A}$, adrenergic, cholinergic, and dopaminergic receptors.[21]

Nonsteroidal anti-inflammatory drugs such as ketorolac can be beneficial in status migrainosus; in the intravenous form, ketorolac has the highest bioavailability. However, ketorolac can cause gastritis. $D_2$ receptor antagonists such as metoclopramide, prochlorperazine, promethazine, and chlorpromazine are used as antiemetics to treat nausea and vomiting in these attacks. However, there is a risk for a dystonic reaction. Pretreatment with diphenhydramine or benztropine can help prevent extrapyramidal side effects. Magnesium sulfate can have a therapeutic effect at the *N*-methyl-D-aspartate receptor, which can block cortical spreading depression in migraine.[22,23] However, intravenous magnesium can cause hypotension.

Greater occipital nerve blockade has been used for status migrainosus. Corticosteroids may reduce the risk of headache recurrence but are associated with gastritis and, rarely, avascular necrosis. Intravenous valproic acid is an option if there is no contraindication such as liver disease. However, it can cause hyperammonemia in patients taking topiramate. Opioids should be avoided.[24]

**22. D**

Migraine is a condition with complex pathophysiology. Nitric oxide, serotonin (5-HT), and CGRP are all thought to be involved in the pathophysiology of migraine, along with the trigeminovascular system. Interleukin-1 has a role in fever pathophysiology but does not have a role in the production of migraine.[22]

**23. B**

CGRP is a neuropeptide that is a strong vasodilator and plays a role in the pathophysiology of migraine. CGRP is located in the central nervous system and peripheral nervous system and is released prior to and/or during a migraine. The Gepant category of drugs are newer medications (compared to triptans) that can offer acute migraine management without vasoconstriction and thus are safer for patients with a history of coronary artery disease and stroke/transient ischemic attack. They act as CGRP receptor antagonists. The monoclonal antibodies

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against CGRP/receptor are newer medications that have been used for migraine prevention.

5-HT$_{1A}$ receptor antagonists do not have a current role in migraine management. Triptans are 5-HT$_{1B/1D}$ receptor agonists.[17,22]

**24. D**

Familial hemiplegic migraine (FHM) is a rare autosomal dominant condition that results in migraine with aura and hemiplegia. FHM type 1 is linked to chromosome 19p13, associated with the *CACNA1A* gene, and causes abnormalities to the P/Q calcium channel. Patients with this type of FHM can have coma attacks, prolonged hemiplegia, and cerebellar signs such as nystagmus. FHM type 2 is linked to chromosome 1q23 and associated with the *ATP1A2* gene, which leads to defects of the sodium/potassium adenosine triphosphatase ($Na^+/K^+$-ATPase) pump. The symptoms of FHM type 2 include intellectual delay, seizures, prolonged hemiplegia, and coma. FHM type 3 is associated with the 2q24 chromosome and the *SCN1A* gene which results in defects of the presynaptic and postsynaptic voltage-gated sodium channels. The *SCN1A* gene is associated with genetic epilepsy with febrile seizures plus and Dravet syndrome.[25]

**25. D**

This patient likely has a burning sensation due to an injured peripheral nerve.

**26. B**

Sumatriptan is a 5-HT$_{1B/1D}$ receptor agonist.

Most subtypes of serotonin receptors are G protein coupled (including 5-HT$_{1B}$ and 5-HT$_{1D}$). However, the 5-HT$_3$ receptor is a ligand-gated ion channel. Ondansetron is a 5-HT$_3$ antagonist.[17]

**27. D**

Medication-overuse headache is defined as headache that occurs at least 15 days per month in a patient with a history of headache and overuse of medication for longer than 3 months.[1]

Combination medications are prone to causing medication-overuse headache, especially if they contain butalbital. Clonazepam and phenobarbital have been used to treat butalbital withdrawal.

**28. B**

This patient has primary cough headache, which responds to indomethacin. Arnold–Chiari I malformation, which is a common cause of cough headache, needs to be ruled out. Also, cerebrovascular disease and cerebral aneurysms can cause cough headache.[1]

**29.**

1) **B**

2) **C**

3) **A**

4) **D**

5) **E**

*Nociceptive pain* is the term for pain caused by direct activation of pain fibers as a result of tissue injury.

Neuropathic pain results from lesions in the nervous system. Allodynia, hyperalgesia, hyperpathia, dysesthesia, and paresthesias characterize neuropathic pain (see Table 24.4).

*Table 24.4* DEFINITIONS OF PAIN TERMS

| TERM | DEFINITION |
|---|---|
| Allodynia | Pain from a non-noxious stimulus |
| Causalgia | A burning pain occurring after peripheral nerve injury |
| Dysesthesia | Unpleasant sensation (spontaneous or provoked) |
| Hyperalgesia | Pain from a noxious stimulus that is significantly greater than expected |
| Hyperpathia | Delayed, increased pain from a noxious stimulus |

Neuropathic pain tends to be chronic and to increase with time. There is sensitization of nociceptors in patients with neuropathic pain. Nociceptors respond to subthreshold stimuli or have increased response to a typical stimulus. Inflammation contributes to sensitization.[4]

Allodynia is the term used when a person is extremely sensitive to touch and when a non-noxious stimulus causes pain. Trauma, diabetes, chronic opioid use, viral infections such as shingles, and other neurologic conditions have all been cited as potential causes for allodynia.

**30. C**

C and Aδ nerve fibers, which are small fibers, are not assessed with EMG or NCSs. Therefore, EMG and NCSs are not able to diagnose small-fiber neuropathy. EMG and NCSs assess Aα and Aβ nerve fibers.

The gold standard for diagnosis of small-fiber neuropathy is skin biopsy. The intraepidermal nerve fiber density is assessed.[4]

**31. A**

Golgi tendon organs, Meissner's corpuscles, muscle spindles, and Pacinian corpuscles are part of the dorsal column system.

Bare nerve endings are part of the spinothalamic system, which carries pain and temperature information. There are three types of these free endings: mechanoreceptors, thermoreceptors, and polymodal nociceptors. Information from these receptors is transmitted by Aδ and C fibers to the dorsal horn of the spinal cord. (Information from cranial pain afferents travels to the spinal trigeminal nucleus.) Aδ fibers are small and thinly myelinated. They transmit pain and temperature information, typically sharp pain. C fibers are small, unmyelinated nerves that are responsible for slow pain and temperature. They transmit dull pain.

Small-diameter sensory fibers, such as Aδ and C fibers, enter the spinal cord in the tract of Lissauer.

**32. B**

Aδ fibers terminate in lamina I (the marginal zone), lamina II (the substantia gelatinosa), and lamina V in the spinal cord. Aδ fibers transmit pain using glutamate, aspartate, and adenosine triphosphate.

C fibers use substance P and terminate in lamina II. Neurons in lamina II release enkephalins, endorphins, and dynorphins, which inhibit pain transmission.

Axons of second-order neurons responsible for pain sensation decussate in the anterior spinal commissure of the cord and become the spinothalamic tract. The spinothalamic tract projects to the ventral posterolateral thalamus and then to the primary somatosensory cortex.

**33. C**

Mutations in the sodium channel can cause increased pain sensitivity. For instance, mutations in *SCN9A* cause paroxysmal extreme pain disorder and primary erythromyalgia. (Primary erythromyalgia causes episodes of painful, red extremities.) Other mutations in *SCN9A* cause congenital insensitivity to pain. Similarly, some mutations in *SCN11* cause intense pain, and others cause insensitivity to pain. FHM type 3 is caused by sodium channel mutations in *SCN1A*. (FHM type 1 is caused by a calcium channel defect, and FHM type 2 is caused by mutations in $Na^+/K^+$-ATPase pumps.)[4]

**34. A**

Patients with benign paroxysmal torticollis of infancy may develop migraine variants or migraine with aura when older. This condition has been linked to mutations in *CACNA1A*. The same gene is also linked to FHM type 1, spinocerebellar ataxia type 6, and episodic ataxia type 2.

Children with benign paroxysmal torticollis have recurrent episodes of head tilt with pallor, irritability, malaise, vomiting, or ataxia. These children are normal between events.

Cyclic vomiting is also a childhood precursor of migraine.

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# 25.

# PEDIATRIC NEUROLOGY

## QUESTIONS

1. **A neonate with microcephaly and hepatosplenomegaly develops seizures. Computed tomography (CT) shows calcifications surrounding the ventricles. Which of the following organisms is most likely responsible?**
   A. Cytomegalovirus (CMV)
   B. Rubella
   C. Syphilis
   D. Toxoplasmosis

2. **Which type of brachial plexus injury is most common at birth?**
   A. Erb palsy
   B. Middle trunk plexopathy
   C. Klumpke palsy
   D. Complete brachial plexus palsy

3. **A newborn is noted to have facial asymmetry. When she cries, her lower lip is pulled to the lower right. The nasolabial folds are symmetric, and the patient closes both eyes well. What additional test should be performed?**
   A. Echocardiogram
   B. Eye examination
   C. Hearing screen
   D. Head ultrasound

4. **A 3-day-old develops vomiting and diarrhea. On examination, he has hypotonia, cataracts, jaundice, and hepatosplenomegaly. Which of the following diagnoses is most likely?**
   A. Adrenomyeloneuropathy
   B. Arginosuccinase deficiency
   C. Classic galactosemia (type 1)
   D. X-linked adrenoleukodystrophy

5. **A baby in the newborn nursery with a history of poor fetal movements has poor respiratory effort and is hypotonic. His mother has male-pattern baldness, ptosis, and a persistent grip. Which of the following is the preferred confirmatory test?**
   A. Acetylcholine receptor antibodies
   B. DNA methylation
   C. Molecular genetic testing of the gene *DMPK*
   D. Electromyography

6. **A mother brings her infant son to the emergency department because she has noticed that he has brief jerks in his sleep. When she wakes him, they resolve. She has seen the episodes only when the infant is asleep. The patient had a typical event during routine electroencephalography (EEG), and no EEG correlate was seen. The EEG was read as normal. Which of the following is the most likely diagnosis?**
   A. Myoclonic seizures
   B. Benign sleep myoclonus
   C. Self-limited epilepsy with centrotemporal spikes
   D. Tics

7. **Which of the following statements is *false*?**
   A. The majority of newborns with stroke have focal deficits at birth.
   B. Placental vasculopathy can cause perinatal acute ischemic stroke.
   C. Most neonatal strokes involve the left middle cerebral artery territory.
   D. In most cases, antithrombotic therapy is not indicated for perinatal stroke.
   E. Hemi-clonic seizures raise concern for perinatal arterial ischemic stroke.

8. **An infant with a cranial bruit over the posterior cranium and bounding carotid pulses develops congestive heart failure. What is the most likely cause?**
   A. An arteriovenous malformation
   B. Cardiomyopathy
   C. Hypertension
   D. Carotid stenosis

9. **Which of the following conditions is *least* likely to be associated with cardiac defects?**
   A. DiGeorge syndrome
   B. Menkes disease
   C. Noonan syndrome
   D. Turner syndrome

10. **A 2-week-old with a history of poor feeding develops seizures. On examination, the patient has hypertelorism and a high forehead. He is hypotonic and has poor visual fixation. A bone survey shows calcifications of the patellae. Ultrasound studies show renal cysts. Which of the following is most likely to be present in this condition?**
    A. Increased very-long-chain fatty acids
    B. A cherry-red spot
    C. Blond hair
    D. Renal tubular acidosis

11. **Kernicterus is most likely to cause which of the following?**
    A. Dyskinetic cerebral palsy (CP)
    B. Spastic diplegia

C. Spastic hemiparesis
D. Spastic quadriparesis

**12. A 3-month-old presents with seizures. The seizures do not respond to phenobarbital, fosphenytoin, or levetiracetam. Magnetic resonance imaging (MRI) is normal. Cerebrospinal fluid (CSF) analysis shows two white blood cells, a normal protein level, and a glucose concentration of 30 mg/dL. The serum glucose level is 90 mg/dL. What is the best treatment?**

A. Lacosamide
B. The ketogenic diet
C. Topiramate
D. Zonisamide

**13. A couple brings a baby they have adopted from another country to clinic because of poor feeding and excessive sleepiness. He has large fontanelles, a large tongue, a hoarse cry, and a prominent abdomen with an umbilical hernia. Which of the following diagnoses is suspected?**

A. Beckwith–Wiedemann syndrome
B. Congenital hypothyroidism
C. Cornelia de Lange syndrome
D. Cri du chat syndrome

**14. A 4-month-old is referred because of hypotonia and poor feeding. He is alert and smiling but has limited movement. He does not have facial weakness, but he has tongue fasciculations. Deep tendon reflexes are absent. Sensation is intact. What is the most likely cause?**

A. Acid maltase deficiency
B. An imprinting disorder
C. Mutations in the *SMN1* gene
D. Congenital muscular dystrophy

**15. An infant presents with recent onset of poor feeding and lethargy preceded by constipation. On examination, he has ptosis, his pupils are dilated, and he is weak. The weakness has occurred in a descending pattern. The CSF is normal. Which of the following is the best treatment?**

A. Human botulism immune globulin (BabyBIG)
B. Steroids
C. Intravenous immunoglobulin
D. Plasmapheresis

**16. A 9-month-old child presents with rapid eye movements. The family shows a video of him making a nodding motion with his head. On examination, he has nystagmus and a head tilt. Brain MRI is normal. An EEG that captured his movements was normal. Which of the following is the best next step?**

A. Perform a lumbar puncture for measurement of serotonin metabolites.
B. Order plasmapheresis.
C. Reassure the family.
D. Arrange for video-EEG monitoring.

**17. A 9-month-old presents with flexor spasms. Hypsarrhythmia is seen on the EEG, and the patient is diagnosed with epileptic spasms (infantile spasms). Which of the following is a treatable cause of epileptic spasms?**

A. Phenylketonuria
B. Maple syrup urine disease
C. Isovaleric acidemia
D. All of the above

**18. A 1-year-old is found to have leukocoria on examination. Which of the following is the most likely diagnosis?**

A. Retinoblastoma
B. Septo-optic dysplasia
C. Optic glioma
D. Glaucoma
E. WAGR syndrome

**19. Which of the following statements is *false*?**

A. The most common cause of congenital myasthenic syndromes is defects in the acetylcholine receptor.
B. An incremental response on electromyography (EMG) helps diagnose congenital myasthenic syndromes.
C. Choline acetyltransferase deficiency can cause sudden apnea triggered by stress.
D. Treatments for some congenital myasthenic syndromes can worsen other types of congenital myasthenic syndromes.
E. Fluoxetine and ephedrine have been used to treat certain congenital myasthenic syndromes.

**20. A 1-year-old boy presents with developmental regression. He is hypotonic and has decreased reflexes on examination. His sister had similar symptoms and progressed to visual impairment and spastic tetraplegia. Her conjunctival, skin, and nerve biopsies showed spheroid bodies. What is the diagnosis?**

A. Infantile neuroaxonal dystrophy
B. Krabbe disease
C. Subacute sclerosing panencephalitis
D. Unverricht–Lundborg disease

**21. An 18-month-old child is brought to the clinic for speech delay. He started babbling at 14 months but does not say any words. He began pointing at objects at 16 months but has not done so in the past few weeks. He has never waved bye-bye. Which of the following steps would *not* be appropriate at this time?**

A. Hearing screen and referral for speech therapy evaluation
B. Lead screening if a history of pica is obtained
C. Lumbar puncture for lactate, amino acids, and neurotransmitters
D. Screening for autism

**22. A 2-year-old presents with fever and a 4-minute generalized tonic–clonic seizure. On examination, he has otitis media bilaterally. He has no meningeal signs, and his neurologic examination is normal. Which of the following is recommended?**

A. MRI
B. EEG
C. A comprehensive metabolic profile
D. A lumbar puncture should be considered if the child was pretreated with antibiotics.

**23. A 3-year-old presents with episodes of decreased responsiveness and posturing. They occur most often when the child is sitting in a car seat. During an episode, she rocks her body. She does not respond the first time her name is called but does respond to touch. The event stops if she is removed from the car seat. The birth history and past medical history are unremarkable. Development is normal. The physical examination is normal. EEG is normal. What is the most likely diagnosis?**

A. Childhood absence epilepsy
B. Dystonia
C. Infantile self-gratification syndrome
D. Sandifer syndrome

**24. A 4-year-old presents with irritability and difficulty walking 5 days after spending time in the woods. He develops an ascending paralysis with areflexia. CSF and repetitive nerve stimulation are normal. Which of the following is recommended first?**

A. Intravenous immunoglobulin
B. Steroids
C. Plasmapheresis
D. A thorough skin and hair evaluation, especially the scalp

**25. A 1-year-old is brought to the clinic because he has episodes of crying to the point of loss of consciousness. The events occur when the patient injures himself. The birth and developmental histories are normal. The physical examination is normal. An electrocardiogram (ECG) is normal. What is the most likely diagnosis?**

A. Breath-holding spells
B. Hyperekplexia
C. Periodic paralysis
D. Intermittent explosive disorder

**26. A 6-year-old and a 50-year-old are both in the emergency department for stroke. Which of the following statements is *false*?**

A. Children with acute stroke usually present with hemiparesis.
B. Most children presenting with acute stroke-like symptoms are found to have a stroke mimic.
C. If a child with stroke presents with a seizure, the stroke is likely to be hemorrhagic.
D. Due to more rapid hepatic clearance, the child is expected to clear tissue plasminogen activator faster than the adult.

**27. A child has a left basal ganglia infarction and stenosis at the junction of the distal internal carotid artery, proximal anterior cerebral artery, and proximal middle cerebral artery on the left. Later, repeat imaging indicates that the narrowing is no longer present. The child had a viral illness 3 months before the stroke but otherwise is healthy. Which of the following diagnoses should be suspected?**

A. Carotid dissection with emboli
B. Endocarditis with emboli
C. Moyamoya disease
D. Transient cerebral arteriopathy

**28. A child presents with fever, confusion, and seizures that are difficult to control. The physical examination is remarkable for cervical lymphadenopathy. CSF, CT, and MRI findings are normal. What is the most likely etiology?**

A. *Bartonella henselae*
B. CMV
C. Herpes simplex virus
D. Toxoplasmosis

**29. Which of the following diseases is *least* likely to be associated with anterior temporal cysts?**

A. Perinatal herpes simplex virus infection
B. Menkes disease
C. Megalencephalic leukodystrophy with subcortical cysts
D. Fabry disease

**30. Which of the following diseases is *least* likely to be associated with macrocephaly?**

A. Achondroplasia
B. Mowat–Wilson syndrome
C. Neurofibromatosis type 1
D. Sotos syndrome

**31. Which of the following conditions is *least* likely to be associated with skeletal abnormalities?**

A. Coffin–Lowery syndrome
B. Down syndrome
C. Maple syrup urine disease
D. Rubenstein–Taybi syndrome
E. Klippel–Feil syndrome

**32. Which cause of progressive myoclonic epilepsy results from a dodecamer repeat expansion in the *CSTB* gene?**

A. Unverricht–Lundborg disease
B. Lafora body disease
C. Sialidosis type I
D. Infantile neuronal ceroid lipofuscinosis (NCL)

**33. A 6-year-old boy presents with repetitive, nonrhythmic shoulder shrugging. He says he usually is not aware of it. He says that he can briefly control it when he realizes it is occurring. His mother states that no one else has noticed the shoulder shrugging, and it does not disturb her or the patient. What is the next step?**

A. Reassure the mother.
B. Start clonidine.
C. Start risperidone.
D. Start guanfacine.

**34. An 8-year-old presents with paroxysmal events. His mother says that the child loses consciousness and then has generalized jerking. These episodes occur when he is exercising or scared. He started having more episodes after being prescribed methylphenidate for attention-deficit/hyperactivity disorder. His paternal aunt and uncle both had syncope and died suddenly in their twenties. Which of the following is most likely to yield the diagnosis?**

A. ECG
B. EEG
C. Echocardiogram
D. Tilt table test

**35. An 11-year-old boy presents with recent onset of bilateral leg weakness and urinary incontinence. What is the next diagnostic step?**

A. Stat MRI of the spine
B. EMG and nerve conduction studies
C. Muscle biopsy
D. Muscular dystrophy genetic panel

**36. A 13-year-old girl briefly loses consciousness whenever her blood is drawn. ECG, echocardiogram, and Holter findings are normal. What is the most likely diagnosis?**

A. Orthostatic hypotension
B. Psychogenic nonepileptic seizures (PNES)
C. Postural orthostatic tachycardia syndrome
D. Vasovagal syncope

**37. A 15-year-old boy presents with complaints of falls from his skateboard. His examination is unremarkable except for mild ataxia. Imaging demonstrates a cystic mass with an enhancing nodule in the right cerebellar hemisphere. Which of the following is the most likely diagnosis?**

A. Ependymoma
B. Medulloblastoma
C. Oligodendroglioma
D. Pilocytic astrocytoma

**38. Which of the following is the most common primary cord neoplasm in children?**

A. Astrocytoma
B. Ependymoma
C. Hemangioblastoma
D. Ganglioglioma

**39. A 15-year-old girl presents with intractable epilepsy. Her seizures started 2 years ago, approximately 1 month after her father's death. She has generalized shaking for longer than 1 hour. Previous EEGs performed immediately after her seizures have been normal. She has failed treatment with levetiracetam, lamotrigine, topiramate, and lacosamide. She is referred to the epilepsy monitoring unit, where she has an event with asynchronous jerking movements. During the event, her phone rings, and the movements pause briefly and then resume. What is the most likely diagnosis?**

A. Frontal lobe epilepsy
B. Juvenile myoclonic epilepsy
C. Temporal lobe epilepsy
D. Psychogenic nonepileptic seizures

**40. A 15-year-old patient has been having academic difficulties. His mother says he has not been acting like himself. She has also seen quick jerking movements. EEG shows background slowing and generalized periodic discharges occurring every 4 seconds. CSF analysis shows oligoclonal bands. Which of the following is *least* likely to be found in this condition?**

A. Cowdry B bodies
B. Demyelination and gliosis
C. Measles antibodies in the CSF
D. Progression to dementia

**41. Which of the following is *least* likely to be helpful in treating spinal muscular atrophy (SMA)?**

A. Cerliponase alfa
B. Nusinersen
C. Onasemnogene abeparovec-xioi
D. Risdiplam

**42. A 5-year-old presents with right arm weakness and areflexia after an upper respiratory infection. Sensation is normal. He tests positive for enterovirus D68. Which of the following findings is most likely to be found on spine MRI?**

A. Enlarged central canal
B. Increased T2 signal in the posterior columns
C. Increased T2 signal in the cervical gray matter
D. Hemi-cord swelling with greater involvement of the white matter than the gray matter

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# PEDIATRIC NEUROLOGY

## ANSWERS

**1. A**

There are multiple causes of seizures in the neonate. The most common cause in the first 24 hours of life is hypoxic–ischemic encephalopathy. It is also important to exclude sepsis and bacterial meningitis. Intrauterine infection is a less common cause of seizures.

CMV is the most common intrauterine viral infection. CMV can cause microcephaly, migration defects, intracerebral calcifications, retinitis, and sensorineural hearing loss. Systemic symptoms of CMV infection include petechiae, an elevated direct hyperbilirubinemia, and hepatosplenomegaly.

The calcifications in patients with CMV infection surround the ventricle. Intracerebral calcifications are also seen in congenital toxoplasmosis, but they tend to be diffusely distributed.

**2. A**

Erb palsy (upper trunk plexopathy) is the most common brachial plexus injury in the newborn. Large infants with shoulder dystocia are at increased risk. Erb palsy is characterized by a "waiter's tip" posture. C5-, C6-, and sometimes C7-innervated muscles are affected. The child has weakness of the deltoid muscle, affecting abduction; the infraspinatus, affecting external rotation; the biceps and brachioradialis muscles, affecting flexion; and the supinator muscle. Therefore, the arm is adducted and internally rotated, and the elbow is extended and pronated. The biceps reflex is absent.

Klumpke palsy affects muscles innervated by C8 and T1 nerve roots.

A complete brachial plexus palsy may be accompanied by Horner syndrome.

**3. A**

This patient has Cayler syndrome, which is also known as Cayler cardiofacial syndrome. It is characterized by hypoplasia of the depressor anguli oris muscle and congenital heart defects such as ventricular septal defects or tetralogy of Fallot. An echocardiogram should be performed.

**4. C**

This patient has classic galactosemia, which is caused by mutations in the *GALT* gene. This gene encodes galactose-1-phosphate uridyltransferase. Classic galactosemia manifests in the newborn period with vomiting, jaundice, lethargy, and a bleeding diathesis after exposure to breast milk or formulas containing lactose. Children with classic galactosemia are prone to *Escherichia coli* sepsis. Cataracts develop. Intellectual disability is also a complication of classic galactosemia that is untreated.

Adrenomyeloneuropathy, arginosuccinase deficiency, and X-linked adrenoleukodystrophy do not usually manifest in the neonatal period.

**5. C**

This patient has congenital myotonic dystrophy, which is a form of myotonic dystrophy type I. It is usually inherited from the mother. Congenital myotonic dystrophy manifests with hypotonia and weakness at birth. Facial weakness, respiratory insufficiency, poor feeding, clubfoot, and decreased reflexes may also occur in neonates with congenital myotonic dystrophy. In this case, the mother's features aid in the diagnosis. Adults with myotonic dystrophy type I tend to have male-pattern baldness, facial weakness, ptosis, and myotonia. The mother's persistent grip is caused by myotonia. Myotonia can be found on EMG in adults with myotonic dystrophy but is not present in newborns. Newborns can be diagnosed with gene testing. Myotonic dystrophy type I is caused by expansion of the CTG repeat in the *DMPK* gene, which is on chromosome 19. Myotonic dystrophy type I is autosomal dominant and demonstrates anticipation.

DNA methylation is one technique used to diagnose Prader–Willi syndrome, which is a cause of neonatal hypotonia. In patients with Prader–Willi syndrome, methylation studies demonstrate the absence of paternally imprinted genes at chromosome 15q11-13.

Neonates born to mothers with myasthenia gravis can have transient neonatal myasthenia gravis due to maternal autoantibodies. These infants have weakness, hypotonia, difficulties with feeding, and respiratory depression.

**6. B**

This patient has benign sleep myoclonus, which is a normal condition. It is characterized by quick jerks during sleep. If the infant is awakened, they resolve. The EEG is normal in benign sleep myoclonus.

The EEG is abnormal during myoclonic seizures. Specifically, epileptiform activity is seen.

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**7. A**

Most newborns with stroke do *not* have focal deficits at birth. Later in life, the most common presentation for childhood stroke is hemiparesis, but this usually is not seen in the newborn period. Seizures are a common presentation in neonates. Neonatal stroke may also manifest with encephalopathy and/or apnea. Most neonatal strokes involve the left middle cerebral artery territory, which can present with right-sided hemi-clonic seizures.[1] Although a child who has had a perinatal stroke may not have focal deficits at birth, they may later demonstrate early hand preference due to hemiparesis.

In most cases, antithrombotic therapy is not indicated for perinatal stroke. Exceptions include patients with congenital heart disease or an abnormal prothrombotic workup. Abnormal laboratory results should be repeated at least 3 months later and off treatment to determine whether the abnormality is still present.

**8. A**

This patient has a vein of Galen malformation, which is the most common type of neonatal arteriovenous malformation. Most patients are male. The median prosencephalic vein of Markowski, which normally drains into the vein of Galen, is actually the dilated vein. This vein usually disappears during development but is persistent in patients with a vein of Galen malformation. In the newborn period, vein of Galen malformation typically manifests with congestive heart failure. It can also cause hydrocephalus, ischemia due to a steal phenomenon, or intracranial hemorrhage.

**9. B**

DiGeorge syndrome is a chromosome 22q11.2 deletion syndrome. Velocardiofacial syndrome and Cayler cardiofacial syndrome are also included in this group of disorders. The 22q11.2 deletion syndrome is usually associated with cardiac and palate abnormalities, developmental delay, and immune dysfunction. The term CATCH-22 has been used for these syndromes; CATCH stands for *c*ardiac abnormality, *a*nomalous face, *t*hymus hypoplasia, *c*left palate, and *h*ypocalcemia.

DiGeorge syndrome is caused by abnormal development of the third and fourth pharyngeal pouches and the fourth branchial arch. This causes an abnormal thymus and parathyroid glands, resulting in immune dysfunction and hypocalcemia, respectively. DiGeorge syndrome can manifest with tetany or neonatal seizures due to hypocalcemia.

Noonan syndrome is associated with pulmonary valve stenosis.

Turner syndrome can cause coarctation of the aorta or an abnormal aortic valve.

Menkes disease can cause intracranial hemorrhage due to friable blood vessels, but it does not usually cause cardiac anomalies. Menkes disease can be mistaken for child abuse because of the presence of subdural hygromas and skeletal abnormalities (wormian bones and spurs at the metaphyses).

**10. A**

This is Zellweger syndrome, which is a peroxisomal disorder caused by *PEX* mutations. Children with Zellweger syndrome have characteristic facial features, hypotonia, renal cysts, and calcification of the patellae. Zellweger syndrome can cause a number of cortical abnormalities, and patients are at risk for seizures. Increased levels of very-long-chain fatty acids support the diagnosis. Also, phytanic acid, pristanic acid, and pipecolic acid concentrations may be elevated.

**11. A**

The most common type of CP is spastic CP. Premature infants tend to have spastic diplegia due to periventricular white matter injury.

Causes of dyskinetic CP include hypoxic–ischemic injury and kernicterus (bilirubin encephalopathy). Kernicterus is also associated with high-frequency hearing loss and impaired vertical gaze.

MRI is recommended for evaluation of patients with CP.[2] If a child has hemiplegic CP due to unexplained infarction, then coagulation studies should be considered. An EEG is not required unless there is concern about seizures. Children with CP should be screened for speech and language disorders, vision and hearing impairments, feeding and swallowing difficulties, and intellectual disability. Metabolic and genetic testing are not required for all children with CP but may be considered in certain cases. Indications for potential testing include a lack of perinatal risk factors, a positive family history, onset after a period of normal development, progression of symptoms, regression, fluctuating clinical findings, prominent ataxia, eye movement abnormalities, reduced reflexes, and sensory loss.[3]

**12. B**

This patient has glucose transporter type 1 (Glut-1) deficiency syndrome, also called Glut-1 DS, which results from mutations in the *SLC2A1* gene. *SLC2A1* encodes a glucose transporter in the blood–brain barrier. Glut-1 DS responds to the ketogenic diet.

Mutations in *SLC2A1* can also cause early onset absence epilepsy, alternating hemiplegia of childhood, paroxysmal choreoathetosis with episodic ataxia and spasticity (DYT9), and epilepsy with exercise-induced dyskinesia (DYT18).

**13. B**

This child has congenital hypothyroidism. Congenital hypothyroidism is associated with prolonged physiologic jaundice, poor feeding, increased sleep, constipation, large fontanelles, macroglossia, and an umbilical hernia. Lack of treatment can cause neurologic complications such as intellectual disability.

Down syndrome is also associated with macroglossia and enlarged fontanelles that are slow to close. Hypothyroidism can occur in Down syndrome.

Beckwith–Wiedemann syndrome also causes macroglossia and an umbilical hernia, but it is associated with macrosomia. It is an overgrowth disorder. Growth may be asymmetric, causing hemihyperplasia. Patients with Beckwith–Wiedemann syndrome may be born with an omphalocele. Neonatal hypoglycemia may result from hyperinsulinism. Visceromegaly can occur in this condition. Patients with Beckwith–Wiedemann syndrome are at risk for tumors such as Wilms tumor and hepatoblastoma. Beckwith–Wiedemann syndrome is an imprinting disorder.

Cornelia de Lange syndrome causes intrauterine growth retardation, characteristic facial features, and skeletal abnormalities. Infants have a low-pitched cry similar to a growl.

Cri du chat syndrome is caused by partial deletion of chromosome 5p. It is associated with a high-pitched cry similar to that of a cat, microcephaly, distinctive facial features, and developmental delay.

**14. C**

This patient has spinal muscular atrophy type 1 (SMA I), which is also known as Werdnig–Hoffman disease. Motor neuron loss occurs in the anterior horn.

SMA, which is autosomal recessive, is most often caused by mutations in *SMN1* on chromosome 5q. *SMN1* and *SMN2* encode for survival motor neuron protein, but *SMN1* produces more functional protein. *SMN2* modifies the severity of SMA; more copies of *SMN2* result in less severe disease.

SMA I is the most severe form of SMA. Without treatment, patients never sit, and they develop aspiration and respiratory insufficiency. Death occurs at approximately age 2 years. Patients with SMA II are able to sit but have difficulty walking. Finger tremor may be present. Patients with SMA III (Kugelberg–Welander disease) are able to walk. Onset of symptoms occurs after age 1 year. SMA IV manifests in adulthood.

Acid maltase deficiency causes Pompe disease, which is glycogen storage disease type 2. Infantile-onset Pompe disease can cause neonatal hypotonia and weakness. These patients can also have macroglossia and congestive heart failure.

Imprinting disorders are responsible for Prader–Willi, Angelman, Beckwith–Wiedemann, and Russell–Silver syndromes. Prader–Willi syndrome manifests with hypotonia in neonates, but tongue fasciculations do not occur. Newborns with Prader–Willi syndrome tend to be lethargic, not alert.

Congenital muscular dystrophy can cause weakness and hypotonia in neonates, but tongue fasciculations are more characteristic of SMA.

**15. A**

This patient has infantile botulism. Infantile botulism is caused by ingestion of *Clostridium botulinum* spores, which produce toxin in the gastrointestinal tract. Infantile botulism is associated with ingestion of honey, but this is not the only cause. Spores can also be found in soil. The toxin from the spores causes decreased acetylcholine release. Constipation is typically the first symptom. Then a descending weakness occurs. Autonomic dysfunction and respiratory failure can ensue. Stool cultures help provide the diagnosis. EMG can also support the diagnosis. Rapid repetitive nerve stimulation can cause an incremental response. Treatment is with human botulism immune globulin (BabyBIG).

In wound botulism, the wound is infected by spores, and toxin is produced in the wound.

Foodborne botulism is caused by ingestion of food that contains the botulism toxin, which is produced by the bacteria *C. botulinum*. It is associated with vomiting and diarrhea, as well as neurologic symptoms.

Botulism can imitate acute inflammatory demyelinating polyradiculoneuropathy (AIDP), which is the most common type of Guillain–Barré syndrome (GBS). However, in botulism, descending weakness occurs, and the CSF is normal. GBS causes ascending weakness and albuminocytologic dissociation in the CSF. EMG and nerve conduction studies also help differentiate the conditions.

**16. C**

This patient most likely has spasmus nutans, which is characterized by nystagmus, head nodding, and a head tilt. Onset is usually during the first year of life. Spasmus nutans self-resolves in a couple of years. The differential diagnosis includes glioma of the optic nerve or chiasm, third ventricle tumor, Leigh disease, Pelizaeus–Merzbacher disease, and vermian hypoplasia.

Opsoclonus–myoclonus–ataxia syndrome (OMAS), which can be associated with neuroblastoma, is also in the differential. These patients have chaotic eye movements rather than nystagmus. Myoclonus and ataxia also help differentiate this syndrome from spasmus nutans; however, not all patients with OMAS have all the symptoms.

**17. D**

Certain organic acidurias and amino acidopathies can cause epileptic spasms. Phenylketonuria, maple syrup urine disease, and isovaleric acidemia can cause epileptic spasms and are treated with special restricted diets. Patients with epileptic spasms due to pyridoxine dependency should be treated with pyridoxine. Likewise, biotinidase deficiency can cause epileptic spasms and should be treated with biotin. Patients with epileptic spasms due to glucose transporter type 1 deficiency syndrome benefit from treatment with the ketogenic diet. The developmental delay, epilepsy, neonatal diabetes (DEND) syndrome also causes epileptic spasms. It results from mutations in a potassium channel gene. These patients benefit from treatment with sulfonylurea. Other metabolic causes of epileptic spasms are Menkes disease, nonketotic hyperglycinemia, and mitochondrial disease.

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**18. A**

Retinoblastoma is the most common primary intraocular tumor in children. It is an embryonal solid tumor with small round blue cells. The term primitive neuroectodermal tumor (PNET) is no longer used, but it was in this group. It is caused by a mutation on chromosome 13. It can manifest with leukocoria or strabismus. Patients with retinoblastoma can also have pineoblastoma or osteosarcoma. Flexner–Wintersteiner rosettes (real rosettes) are seen on histology.

"WAGR" in WAGR syndrome stands for *W*ilms tumor, *a*niridia, *g*enitourinary anomalies, and mental *r*etardation. (In general, the term intellectual delay or intellectual disability is now preferred over the term mental retardation.)

**19. B**

The most common cause of congenital myasthenic syndromes is defects in the acetylcholine receptor, followed by mutations that affect the endplate.

Patients with congenital myasthenic syndromes tend to have fatigable weakness. A decremental response is seen on EMG. Single-fiber EMG may also aid in the diagnosis. Congenital myasthenic syndromes can also manifest with arthrogryposis at birth. (Arthrogryposis occurs in multiple conditions. It is associated with reduced fetal movement.)

Patients with choline acetyltransferase deficiency, which is one of the presynaptic causes of congenital myasthenic syndrome, can present with apnea after stress. Some patients with choline acetyltransferase deficiency present at birth with hypotonia and apnea.

Pyridostigmine is helpful for some congenital myasthenic syndromes, including choline acetyltransferase deficiency, but it may be harmful for other congenital myasthenic syndromes, such as acetylcholinesterase deficiency, slow-channel syndrome, and laminin-$\beta_2$ deficiency. Some congenital myasthenic syndromes are treated with adrenergic agonists. For instance, laminin-$\beta_2$ deficiency has been treated with ephedrine. Slow-channel syndrome has been treated with quinine, quinidine, and fluoxetine.[4]

**20. A**

This patient has infantile neuroaxonal dystrophy, which manifests with developmental delay but then causes regression. It affects the central and peripheral nervous systems. Hypotonia evolves into spasticity, and optic atrophy occurs. Neuropathy may result in limb mutilation. Autonomic dysfunction causes urinary retention and decreased tearing. Hypothalamic dysfunction can result in diabetes insipidus or hypothyroidism. Seizures may occur. MRI shows cerebellar atrophy. Some patients have iron accumulation in the basal ganglia. Spheroid bodies are found on nerve biopsy. Infantile neuroaxonal dystrophy is caused by mutations in the *PLA2G6* gene. This gene encodes A2 phospholipase, which is necessary for metabolizing phospholipids. Mutations in the *PLA2G6* gene also cause neurodegeneration with brain iron accumulation 2B and Parkinson disease 14 (PARK 14).

Krabbe disease, which is also known as globoid cell leukodystrophy, also manifests in infancy and affects the central and peripheral nervous systems. Krabbe disease is a lysosomal storage disease caused by deficiency of galactocerebrosidase (also known as galactosylceramidase or galactosylceramide β-galactosidase). Krabbe disease usually manifests before 6 months of age with irritability, fever, and sensitivity to external stimuli. It also causes spasticity, optic atrophy, and neuropathy. Nerve conduction velocities are reduced, and nerve biopsy specimens contain deposits of sphingolipids. CSF protein is elevated, and MRI shows increased T2 signal in the white matter.

Subacute sclerosing panencephalitis and Unverricht–Lundborg disease are discussed later.

**21. C**

The initial evaluation should include a hearing screen and developmental assessment. Lead screening should be performed if there is a history of pica or if there has been a possible exposure to lead.

This child may have autism. Lumbar puncture is not part of the initial testing. Symptoms that raise concern for a metabolic cause of autism include acid–base disturbances, anemia, skin changes, hypotonia, multisystem involvement, poor growth, microcephaly, and seizures.[5]

Children who have difficulty with verbal and nonverbal social communication who do not have restricted interests and behaviors may have social communication disorder.

**22. D**

This patient most likely had a simple febrile seizure.

Pretreatment with antibiotics can mask the signs of meningitis; therefore, a lumbar puncture should be considered in patients on antibiotics who present with what appears to be a simple febrile seizure (see Box 25.1).[6]

### *Box 25.1* AMERICAN ACADEMY OF PEDIATRICS GUIDELINES REGARDING MANAGEMENT OF A SIMPLE FEBRILE SEIZURE

- The cause of the fever should be investigated. Meningitis should be considered.
- If the child appears ill or the history or physical examination is concerning for meningitis, a lumbar puncture should be performed.
- In a child between ages 6 and 12 months, a lumbar puncture "is an option" if the child could be deficient in immunizations for *Haemophilus influenzae* type b or *Streptococcus pneumoniae*.
- A lumbar puncture "is an option" if the child was pretreated with antibiotics, which can mask signs and symptoms of meningitis.
- Laboratory studies, such as a comprehensive metabolic profile and complete blood count, are not routinely necessary.
- Neuroimaging and EEG are not routinely necessary.

A febrile seizure is a seizure that occurs in a child between ages 6 and 60 months without a central nervous system infection with a temperature of 100.4°F (38°C) or higher by any method. A simple febrile seizure lasts less than 15 minutes, is generalized, and does not recur. A complex febrile seizure is focal, lasts 15 minutes or longer, or recurs within 24 hours.

The strongest predictor of febrile seizure recurrence is age younger than 12–16 months.[7] Other predictors of febrile seizure recurrence are a history of febrile seizures in a first-degree relative, low fever in the emergency room, and brief time between fever onset and the seizure.[7] These factors do *not* predict risk for epilepsy. Regarding risk for epilepsy after a febrile seizure, patients with neurological problems and patients with complex febrile seizures are at higher risk for epilepsy.[7]

The consequences of *prolonged* febrile seizures are being investigated. The Consequences of Prolonged Febrile Seizures in Childhood (FEBSTAT) study is a prospective, multicenter study designed to investigate the acute and long-term consequences of febrile status epilepticus, which was defined as a febrile seizure or series of seizures lasting longer than 30 minutes (see Box 25.2).[8–12]

### *Box 25.2* FINDINGS OF THE CONSEQUENCES OF PROLONGED FEBRILE SEIZURES IN CHILDHOOD (FEBSTAT) STUDY

- Children with febrile status epilepticus (FSE) are at risk for acute hippocampal injury, and a substantial number also have abnormalities in hippocampal development.
- Findings of focal slowing or attenuation are present in EEGs obtained within 72 hours in a substantial proportion of children with FSE and are highly associated with MRI evidence of acute hippocampal injury.
- FSE rarely causes CSF pleocytosis, so CSF pleocytosis should not be attributed to FSE.
- Human herpesvirus type 6 (HHV-6) is a common cause of febrile seizures and can cause FSE. HHV-7 infection is less often associated with FSE. Together, they account for one-third of FSE cases.
- Earlier treatment of FSE resulted in shorter seizure duration.

**23. C**

This patient most likely has infantile self-gratification syndrome, which previously was called infantile masturbation. This is a benign condition.

Sandifer syndrome is posturing caused by gastroesophageal reflux.

Childhood absence epilepsy would manifest with absence seizures in multiple settings, and the EEG would be abnormal.

Improvement with distraction is more characteristic of infantile self-gratification syndrome than of dystonia.

**24. D**

This patient has tick paralysis. The tick often attaches to the scalp and can be detected by a thorough evaluation. Tick paralysis causes ataxia and an ascending flaccid paralysis. This can progress to cause ptosis, ophthalmoplegia, bulbar paralysis, quadriplegia, and respiratory failure if the tick is not removed. Removal of the tick early in the course results in neurologic improvement within a day or so.

Tick paralysis is in the differential diagnosis for AIDP. AIDP is usually associated with albuminocytologic dissociation (an elevated protein level and normal white blood cells) in the CSF.

**25. A**

This patient has breath-holding spells. These occur in infants and improve by school age. The events are typically triggered by fear, pain, or frustration. The child cries and then holds his breath in expiration. He may lose consciousness and become limp. Some children have clonic activity. Patients with breath holding who are iron deficient may respond to iron supplementation. Some children without iron deficiency improve with iron supplementation.

Breath-holding spells have been divided into cyanotic and pallid-type events based on the color of the child during the event. Pallid breath-holding spells may be related to excessive vagal tone.

**26. C**

Whereas a seizure in an adult suggests there is a higher likelihood that the stroke is hemorrhagic, it is not predictive in the child. Most children with acute stroke present with hemiparesis. However, most children with stroke-like symptoms do not have stroke.

**27. D**

This child has transient cerebral arteriopathy or focal arteriopathy, which can be seen with varicella-zoster virus and other infectious agents. Varicella tends to affect the M1 segment of the middle cerebral artery.

**28. A**

This is cat-scratch disease, which is caused by *B. henselae*. *Bartonella* can cause encephalitis, retinitis, meningitis, transverse myelitis, and a syndrome resembling AIDP. *Bartonella* neuroretinitis can mimic optic neuritis. Lipid exudate in the macula can cause a macular star in patients with *Bartonella*, but this may not initially be present.[13] Cervical lymphadenopathy also aids in the diagnosis of cat-scratch disease.

**29. D**

Perinatal herpes simplex virus infection, Menkes disease, and megalencephalic leukodystrophy with subcortical cysts all can cause anterior temporal cysts.

**30. B**

Achondroplasia, neurofibromatosis type 1, and Sotos syndrome cause macrocephaly.

Mowat–Wilson syndrome causes microcephaly. Other features of Mowat–Wilson syndrome are agenesis of the corpus callosum and Hirschsprung disease.

Sotos syndrome causes megalencephaly and gigantism.

Alexander disease, Canavan disease, GM2 gangliosidoses (Tay–Sachs disease and Sandhoff disease), mucopolysaccharidoses, glutaric aciduria type 1, and megalencephalic leukoencephalopathy with subcortical cysts are metabolic causes of megalencephaly.

Linear nevus syndrome and tuberous sclerosis complex can cause hemimegalencephaly. Klippel–Trenaunay syndrome, Proteus syndrome, and hypomelanosis of Ito can cause hemimegalencephaly with somatic hemihypertrophy. Proteus syndrome is caused by a mutation in *PTEN*, which is a tumor suppression gene.

**31. C**

Maple syrup urine disease is the least likely to be associated with skeletal abnormalities.

Patients with Down syndrome can have atlantoaxial instability.

Rubenstein–Taybi syndrome has also been called broad thumb–hallux syndrome. It is caused by mutations in the gene *CREBBP*, which encodes CREB binding protein. This protein is in the family of chromatin-modifying enzymes and regulates cell growth and division. Rubenstein–Taybi syndrome causes microcephaly, characteristic facial features, micrognathia, a highly arched palate, and broad thumbs and great toes. Some patients have parietal foramina.

Coffin–Lowry syndrome is a cause of X-linked intellectual disability. It results from mutations in the *RSK2* gene, which is in the Ras-MAPK pathway. Patients with Coffin–Lowry syndrome have microcephaly, a thickened calvarium, sensorineural hearing loss, kyphoscoliosis, and beaking of the vertebrae. A pectus deformity may also be present.

Klippel–Feil syndrome is associated with abnormal fusion of cervical vertebrae.

**32. A**

Unverricht–Lundborg disease, Lafora body disease, sialidosis type I, and infantile NCL all cause progressive myoclonic epilepsy.

Unverricht–Lundborg disease (EPM1) typically results from a dodecamer repeat expansion in the *CSTB* gene, which encodes cystatin B. The first symptom in most patients is myoclonic jerks. Generalized tonic–clonic seizures are also a common presentation. The onset is typically between ages 6 and 15 years. Ataxia occurs later.

**33. A**

This is a motor tic. Becaue it is not bothering anyone or causing social problems, no treatment is needed.

**34. A**

This patient has long QT syndrome, which can be mistaken for epilepsy. Stress and exercise can trigger arrhythmia in these patients, and stimulants should be avoided.

A normal routine ECG does not rule out long QT syndrome. A Holter monitor may be needed for diagnosis.

**35. A**

Bilateral leg weakness and urinary incontinence raise concern for a spinal cord lesion, which is an emergency. A stat MRI can confirm the diagnosis.

**36. D**

This patient has vasovagal syncope, which is characterized by brief loss of consciousness due to a decrease in blood pressure triggered by pain or stress. Accompanying symptoms include dizziness/lightheadedness, nausea, blurred or constricted vision, paleness, and diaphoresis.

**37. D**

The imaging findings are consistent with pilocytic astrocytoma, which is the most common glioma in children. Most pilocytic astrocytomas occur in the cerebellum, but they can be found in supratentorial sites such as the optic pathway or hypothalamus.

Other tumors can also have the appearance of a cyst with an enhancing mural mass. These include gangliogliomas, pleomorphic xanthoastrocytoma, and hemangioblastomas. If this patient had Von Hippel–Lindau syndrome, his mass would most likely be a hemangioblastoma.

**38. A**

The most common primary cord neoplasm in children is astrocytoma.

**39. D**

This patient has PNES. PNES are in the differential for intractable epilepsy. Video-EEG is the gold standard for diagnosis. Often, patients with PNES have suffered significant emotional trauma. Counseling is the treatment.

**40. A**

This is subacute sclerosing panencephalitis, which is a neurodegenerative disease caused by remote measles infection. It manifests with academic deterioration and changes in personality. Patients develop seizures and myoclonic jerks. They eventually develop dementia. The EEG shows a characteristic periodic pattern. Elevated anti-measles antibodies (immunoglobulin G) are found in the serum and CSF. Oligoclonal bands can be seen in the CSF. Intranuclear Cowdry A bodies are seen within cells in the brain.

Cowdry B bodies are associated with polio.

**41. A**

Cerliponase alfa is an intrathecal medication used to treat NCL type 2, which is due to deficiency of tripeptidyl peptidase 1.

Nusinersen, onasemnogene abeparovec-xioi, and risdiplam are treatments for SMA.

**42. C**

This patient has acute flaccid myelitis, which is an anterior horn syndrome that causes T2 hyperintensity in the gray matter of the spinal cord.[14,15] The lesions may be longitudinally extensive and can be associated with edema and white matter involvement.[14]

An enlarged central canal can be associated with central cord syndrome, which is characterized by a suspended level with loss of pain and temperature due to involvement of decussating spinothalamic tracts.

Syphilis and HIV can affect the posterior columns.[15] Expected clinical findings are decreased vibration and proprioception below the level of the lesion.

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# 26.

# PSYCHIATRY

## QUESTIONS

**1. In the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) and the fifth edition, text revision of the DSM (DSM-5-TR), if a physician believes strongly that a patient will meet the full criteria for a diagnosis, the patient can be diagnosed with the condition using which of the following qualifying terms?**

A. Anticipated
B. Assumed
C. Predicted
D. Provisional

**2. In the DSM-5 and DSM-5-TR, a 7-year-old patient would be diagnosed with which of the following instead of "mental retardation"?**

A. Developmental delay not otherwise specified
B. Global cognitive impairment
C. Global developmental delay
D. Intellectual disability/intellectual developmental disorder

**3. In the DSM-5 and DSM-5-TR, a patient with impaired social interaction and stereotyped behaviors, who previously would have been diagnosed with Asperger disorder, would be diagnosed with which of the following conditions?**

A. Asperger disorder
B. Autism spectrum disorder
C. Pervasive developmental delay not otherwise specified
D. Pervasive developmental delay spectrum

**4. Which of the following statements is *false* regarding the diagnosis of attention-deficit/hyperactivity disorder (ADHD) in the DSM-5 and DSM-5-TR?**

A. Patients with autism spectrum disorder can be diagnosed with ADHD.
B. Symptoms must begin before age 12 years.
C. Patients aged 17 years or older need to meet more criteria to be diagnosed than younger patients do.
D. Symptoms need to be present for at least 6 months.

**5. A 20-year-old patient believes that his neighbor is a spy. He has been convinced of this for 3 months. Despite this belief, the patient is able to function. Apart from avoiding his neighbor, the patient behaves normally. What is the most likely diagnosis?**

A. Brief psychotic disorder
B. Delusional disorder
C. Schizophrenia
D. Schizophreniform disorder

**6. Which of the following statements differentiates brief psychotic disorder from schizophreniform disorder and schizophrenia?**

A. Negative symptoms such as avolition are not part of the criteria for diagnosing brief psychotic disorder.
B. Hallucinations are not part of the criteria for diagnosing brief psychotic disorder.
C. Catatonia is an exclusion criterion for brief psychotic disorder.

**7. How long must the appropriate symptoms be present to meet criteria for a major depressive episode?**

A. 1 week
B. 2 weeks
C. 1 month
D. 2 months

**8. Fill in the blank: In order for an adult to meet criteria for major depressive episode, the patient must have either __________________ or __________________.**

A. Depressed mood or anhedonia
B. Depressed mood or thoughts of death
C. Sleep disturbance or thoughts of death
D. Decreased energy or depressed mood

**9. True or false?**
One major depressive episode is sufficient for the diagnosis of major depressive disorder.

**10. Which of the following statements is *false*?**

A. Children tend to have more problems with weight loss when depressed than adults do.
B. Children with depression may have irritability rather than a depressed mood.
C. Children withdraw more than adults when depressed.
D. Children often have somatic complaints when depressed.

**11. True or false?**
In the DSM-5 and DSM-5-TR, a major depressive episode can be diagnosed in someone who lost a loved one less than 2 months ago.

**12. A woman presents with depressed mood for 2 years. She reports poor concentration, difficulty sleeping, and poor energy during most of this time. She denies thoughts of death or feelings of worthlessness or guilt. She has never had symptoms of hypomania or mania. Which of the following diagnoses is most likely?**

A. Persistent depressive disorder (formerly dysthymia)
B. Cyclothymic disorder
C. Bipolar II disorder
D. Restricted affectivity

13. **True or false?**
In certain circumstances, one may be diagnosed with a manic episode even if it appears to have been triggered by medication, such as starting an antidepressant.

14. **True or false?**
Psychosis is an exclusion criterion for hypomania.

15. **True or false?**
To be diagnosed with bipolar I disorder, one must have had a major depressive episode.

16. **True or false?**
Mania is an exclusion criterion for bipolar II disorder.

17. **Which of the following statements is *false*?**
    A. Risk factors for panic attacks include a tendency to experience negative emotions and smoking.
    B. The tendency to consider anxiety symptoms harmful is a risk factor for panic attacks.
    C. Cannabis can trigger a panic attack.
    D. Repeated panic attacks are sufficient to meet criteria for panic disorder.

18. **A 10-year-old boy is brought to the clinic for rages and aggression at school and at home. These outbursts have been occurring multiple times per week for the past 2 years with minor provocation. He is chronically irritable. What is the most likely diagnosis?**
    A. Disruptive mood dysregulation disorder
    B. Conduct disorder
    C. Oppositional defiant disorder (ODD)
    D. Bipolar II disorder
    E. Intermittent explosive disorder

19. **Which of the following statements is *false*?**
    A. Mood dysregulation is more severe in conduct disorder than in oppositional defiant disorder.
    B. Aggression toward animals is characteristic of conduct disorder but not of oppositional defiant disorder.
    C. Theft is characteristic of conduct disorder but not of oppositional defiant disorder.
    D. Destruction with the intent to intimidate, or to acquire power or money, is characteristic of conduct disorder but not of oppositional defiant disorder.

20. **A 29-year-old woman has seen six gastroenterologists in the past 7 months for severe abdominal pain and nausea. She cannot sleep because she is concerned about the pain. She spends hours on the internet researching this condition. She has undergone an extensive workup, and no abnormalities were found. Which of the following diagnoses is most likely?**
    A. Functional neurologic symptom disorder (conversion disorder)
    B. Illness anxiety disorder
    C. Body dysmorphic disorder
    D. Factitious disorder
    E. Somatic symptom disorder

21. **True or false?**
In the DSM-5, amenorrhea is required for the diagnosis of anorexia nervosa.

22. **True or false?**
Flashbacks are required for the diagnosis of post-traumatic stress disorder (PTSD).

23. **What is the term for the inability to remember information about one's life, especially traumatic events?**
    A. Depersonalization
    B. Derealization
    C. Dissociative identity disorder
    D. Dissociative amnesia

24. **Fill in the blank: A child must be at least _____ years old to be diagnosed with enuresis.**
    A. 3 years old
    B. 5 years old
    C. 8 years old
    D. 10 years old

25. **True or false?**
All paraphilias are mental disorders.

26. **Which of the following disorders is *least* likely to be treated with electroshock therapy (ECT)?**
    A. Catatonia
    B. Depression
    C. Post-traumatic stress disorder (PTSD)
    D. Psychosis

27. **A 30-year-old woman reports that she is having difficulty completing tasks at work despite long hours and dedication to the organization. Her coworkers offer to assist, but she does not trust them to do the work as it should be done. She says she is very detail-oriented and believes strongly in obeying rules. What is her diagnosis?**
    A. Obsessive–compulsive disorder (OCD)
    B. Obsessive–compulsive personality disorder
    C. Histrionic personality disorder
    D. Narcissistic personality disorder

28. **True or false?**
It is possible to have both obsessive-compulsive disorder and obsessive–compulsive personality disorder.

29. **Fill in the blank: Patients with avoidant, dependent, or obsessive–compulsive personality disorders tend to be _______________.**
    A. Dramatic
    B. Eccentric
    C. Anxious
    D. Suspicious
    E. Impulsive

30. **Patients with which of the following personality disorders prefer solitude, do not desire relationships, and appear detached?**
    A. Avoidant
    B. Narcissistic

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C. Schizoid
D. Schizotypal

**31. Which of the following is the most characteristic of borderline personality disorder?**
A. Deceitfulness
B. Lack of remorse
C. Mood instability
D. Arrogance

**32. A patient is diagnosed with an inoperable brain tumor. Instead of grieving, he researches investigational treatments. Which psychological defense is this?**
A. Denial
B. Intellectualization
C. Rationalization
D. Undoing

**33. True or false?**
There are situations in which patient confidentiality should be breached.

**34. A patient with Parkinson disease is diagnosed with depression. A serotonergic medication should *not* be prescribed if the patient is taking which of the following medications?**
A. Pramipexole
B. Ropinirole
C. Selegiline

**35. Which selective serotonin reuptake inhibitor (SSRI) has a short half-life, increasing the risk for a withdrawal syndrome?**
A. Citalopram
B. Fluoxetine
C. Paroxetine
D. Sertraline

**36. What is the mechanism of action of bupropion?**
A. It is a dopamine reuptake inhibitor.
B. It is a norepinephrine reuptake inhibitor.
C. It is a serotonin reuptake inhibitor.
D. A and B
E. B and C

**37. A 20-year-old woman with bulimia is diagnosed with depression. Which of the following antidepressants should be avoided?**
A. Fluoxetine
B. Sertraline
C. Bupropion
D. Escitalopram

**38. Which of the following is a serotonin antagonist and reuptake inhibitor (SARI)?**
A. Duloxetine
B. Mirtazapine
C. Phenelzine
D. Trazodone
E. Viloxazine

**39. Which of the following is *not* usually a side effect of tricyclic antidepressants (TCAs)?**
A. Dry mouth and urinary retention
B. Orthostatic hypotension
C. Memory impairment and delirium
D. QT-interval prolongation on the electrocardiogram (ECG)
E. Insomnia

**40. A 26-year-old man presents with priapism. He says that his psychiatrist warned him that this could occur when he prescribed the medication. Which medication is most likely responsible?**
A. Venlafaxine
B. Bupropion
C. Nefazodone
D. Trazodone

**41. Neuroleptics/conventional antipsychotics treat psychosis by blocking which receptor in the mesolimbic pathway?**
A. $D_1$
B. $D_2$
C. $D_3$
D. $D_4$
E. $D_5$

**42. Which of the following medications is a partial agonist at the $D_2$ and 5-$HT_{1A}$ receptors?**
A. Aripiprazole
B. Olanzapine
C. Quetiapine
D. Valbenazine
E. Ziprasidone

**43. Which antipsychotic demonstrates potent $\alpha_1$ antagonism and causes dose-dependent lengthening of the QT interval?**
A. Iloperidone
B. Lurasidone
C. Paliperidone

**44. Which of the following statements about clozapine is *false*?**
A. Clozapine can be used to treat psychosis in patients with Parkinson disease.
B. Clozapine is associated with a risk for agranulocytosis.
C. Clozapine has a high risk of tardive dyskinesia.
D. Clozapine lowers the seizure threshold.

**45. Which of the following is *not* usually a side effect of lithium?**
A. Hypokalemia
B. Polyuria
C. Hypothyroidism
D. Weight loss

**46. An 18-year-old patient presents with altered mental status, mydriasis, tachycardia, dry mucous membranes, and decreased bowel sounds. Which of the following medications is most likely responsible?**

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A. Amitriptyline
B. Cocaine
C. Fentanyl
D. Meperidine

**47. Which of the following is most likely to cause mania?**

A. Cholinesterase inhibitors
B. β-Blockers
C. Isotretinoin
D. Selegiline

**48. Which of the following is *least* likely to be helpful in treating bipolar disorder in monotherapy?**

A. Carbamazepine
B. Lithium
C. TCAs
D. Valproic acid

**49. For which of the following is cognitive–behavioral therapy *least* helpful?**

A. Autism
B. Bulimia
C. Generalized anxiety disorder
D. Panic disorder

**50. Which of the following is a serotonin partial agonist reuptake inhibitor (SPARI)?**

A. Brexanolone
B. Levomilnacipran
C. Pimavanserin
D. Vilazodone
E. Vortioxetine

# PSYCHIATRY

## ANSWERS

**1. D**

In the DSM-5 and DSM-5-TR, the patient can be given a provisional diagnosis if a physician believes strongly that the patient will ultimately meet full criteria for the diagnosis but not enough information is available to make a firm diagnosis.[1,2]

**2. D**

The terms *intellectual disability* and *intellectual developmental disorder* have replaced the term mental retardation. To be diagnosed with this condition, the onset must be in the developmental period, and the patient must have intellectual and adaptive functioning deficits. Severity is determined by performance in conceptual, social, and practical domains.

The term global developmental delay is used for individuals younger than age 5 years when severity cannot be determined. If a child older than age 5 years cannot be accurately assessed, the term unspecified intellectual disability (intellectual developmental disorder) can be used.

**3. B**

Autism spectrum disorder is characterized by deficits in social communication and interaction and limited, repetitive interests and behaviors. Symptoms start early in development and cause difficulties in functioning. The severity of autism spectrum disorder is classified by the level of support needed, which is determined by the individual's social communication level and behaviors. Language delay is *not* required for the diagnosis of autism spectrum disorder in the DSM-5 or DSM-5-TR.

Children diagnosed with autistic disorder, Asperger disorder, or pervasive developmental delay not otherwise specified based on DSM-IV criteria will most likely be diagnosed with autism spectrum disorder under the DSM-5 and DSM-5-TR criteria.

If a patient has impaired social communication but does not meet the full criteria for autism spectrum disorder, the diagnosis of social (pragmatic) communication disorder should be considered. These patients have difficulty with verbal and nonverbal social communication but do not have restricted interests and behaviors.

Children with impaired speech production or comprehension, such as decreased vocabulary or difficulty forming sentences, beginning in early development are diagnosed with language disorder.

Autism spectrum disorder can be diagnosed in a patient with intellectual disability if the child's social communication is less developed than would be expected for their level of intellectual functioning.

**4. C**

Patients aged 17 years or older need to meet fewer criteria to be diagnosed with ADHD than younger patients do.

For children younger than age 17 years, at least six symptoms of either inattention or hyperactivity and impulsivity, lasting at least 6 months, are still needed for the diagnosis. For patients aged 17 years or older, only five symptoms are needed in the DSM-5 and DSM-5-TR.

In the DSM-5 and DSM-5-TR, ADHD symptoms need to start before age 12 years (instead of age 7 years in the DSM-IV). Patients with autism spectrum disorder can be diagnosed with ADHD.

**5. B**

This patient has delusional disorder, which is characterized by the presence of a delusion for at least 1 month with normal functioning and behavior (except in relation to the delusion). In DSM-IV, delusional disorder was diagnosed if a patient had a nonbizarre delusion for 1 month (and did not meet the criteria for schizophrenia). In the DSM-5 and DSM-5-TR, a patient can be diagnosed with delusional disorder even if the delusion is bizarre. In the DSM-5 and DSM-5-TR, hallucinations can be present in patients with delusional disorder, but they are not prominent, they are related to the delusions, and the patient should not meet criteria for schizophrenia.

**6. A**

To be diagnosed with brief psychotic disorder, one must have at least one of the following: delusions, hallucinations, disorganized speech, or disorganized or catatonic behavior. Symptoms are present for longer than 1 day but less than 1 month and then resolve. Negative symptoms are not one of the criteria. Negative symptoms are included in the diagnostic criteria for schizophrenia and schizophreniform disorder.

Duration of symptoms is the main difference between schizophrenia and schizophreniform disorder. In schizophrenia, symptoms have been present for at least 6 months. In schizophreniform disorder, symptoms have been present for at least 1 month but less than 6 months.

Criterion A for diagnosis of schizophrenia or schizophreniform disorder is the presence of at least two of the following for most of 1 month: delusions, hallucinations, disorganized speech, grossly disorganized behavior or catatonia, and negative symptoms. In DSM-IV, only one of these features was required if the delusions were bizarre or the patient experienced hallucinations in which a voice gave running commentary on the patient or two or more voices spoke to each other. In DSM-5 and DSM-5-TR, this caveat was removed. A new requirement in DSM-5 is that at least one of the two symptoms required for a diagnosis of schizophrenia must be delusions, hallucinations, or disorganized speech. (This is also true in the DSM-5-TR.) Also, in DSM-5 and DSM-5-TR, the subtypes of schizophrenia (e.g., paranoid, disorganized, and catatonic) were removed.

Schizoaffective disorder is diagnosed if there is a major mood disturbance concurrent with Criterion A for schizophrenia and if delusions or hallucinations occur for at least 2 weeks independently of mood disturbance. Symptoms that meet the criteria for a major mood episode are present for the majority of the illness.

7. **B**

Appropriate symptoms must be present for 2 weeks to meet criteria for a major depressive episode.

8. **A**

Five of the appropriate symptoms are required for an adult to meet criteria for a major depressive episode, but one of those symptoms must be depressed mood or anhedonia. Children and adolescents may have an irritable mood instead of a depressed mood. Other symptoms include weight or appetite changes, sleep disturbance, psychomotor agitation or retardation, decreased energy, guilt or feelings of worthlessness, difficulties with attention or decision-making, and thoughts of death. Individuals are considered to have a higher risk for suicide during the 2 years after a suicide attempt.

9. **True**

One major depressive episode is sufficient for the diagnosis of major depressive disorder, but an episode of hypomania or mania excludes this diagnosis.

10. **A**

Children tend to have fewer problems with weight loss when depressed than adults do. In children, consider failure to make expected weight gains.

11. **True**

In the DSM-5 and DSM-5-TR, a major depressive episode can be diagnosed in someone who lost a loved one less than 2 months ago (see Table 26.1).

The DSM-5-TR added the diagnosis prolonged grief disorder. This is in the section of trauma and stress-related disorders. To meet criteria for prolonged grief disorder per the DSM-5-TR, the death must have occurred at least 12 months prior for adults and 6 months prior for children and adolescents. The patient has intense yearning for the deceased and preoccupation with thoughts/memories of the deceased. In addition, the patient has additional symptoms almost every day for 1 month, such as intense emotional pain in relation to the death, emotional numbness, and intense loneliness. In prolonged grief disorder, these symptoms revolve around loss of the deceased rather than a low mood in general in patients with depression.

*Table 26.1* COMPARISON OF BEREAVEMENT AND MAJOR DEPRESSIVE EPISODE

| GRIEF/BEREAVEMENT | MAJOR DEPRESSIVE EPISODE |
|---|---|
| Feelings of emptiness/loss | Depressed mood, anhedonia |
| Decreases with time, "pangs of grief" (waves of feelings when thinking of the deceased) | More persistent depressed mood |
| May have some positive emotions, humor | Self-critical ruminations |
| Self-esteem preserved | Feelings of worthlessness, self-loathing |
| Thoughts of death revolve around joining the deceased | Thoughts of death due to worthlessness, thoughts that death will end one's suffering |

12. **A**

This patient most likely has persistent depressive disorder. This term replaces the terms dysthymia and chronic major depressive disorder in the DSM-5 and DSM-5-TR. To make the diagnosis, mood must have been depressed most of the time for 2 years in adults. In children, the duration is 1 year, and the mood may be irritable rather than depressed (see Boxes 26.1 and 26.2).

In cyclothymic disorder, the patient has a history of symptoms of hypomania and symptoms of depression lasting for at least 2 years in an adult (or 1 year in a child or adolescent) but has never met criteria for a major depressive, manic, or hypomanic episode.

*Box 26.1* FEATURES COMMON TO PERSISTENT DEPRESSIVE DISORDER AND MAJOR DEPRESSIVE DISORDER

- Depressed mood
- Change in appetite
- Change in sleep
- Decreased energy
- Poor self-esteem
- Decreased concentration
- Feelings of hopelessness

### *Box 26.2* CRITERIA FOR MAJOR DEPRESSIVE EPISODE BUT NOT PERSISTENT DEPRESSIVE DISORDER

- Anhedonia
- Psychomotor agitation or retardation
- Feelings of worthlessness or guilt
- Recurrent thoughts of death, suicidal ideation, or suicide attempt or plan

This patient does not meet criteria for bipolar II disorder because she has never had an episode of hypomania.

Restricted affectivity refers to a decreased emotional response.

**13. True**

If the patient's symptoms meet the criteria for mania after the physiologic effect of the medication has worn off, then mania can be diagnosed even if it began with starting an antidepressant.

**14. True**

If a patient meets criteria for hypomania but is psychotic, then the patient has mania, not hypomania. Patients with psychosis due to psychiatric disease can still be oriented to person, place, and time.

Both mania and hypomania are characterized by mood change and change in energy/activity. Also, both diagnoses require four of the other symptoms if the mood is irritable, or three if it is not (see Box 26.3).

### *Box 26.3* FEATURES SEEN IN BOTH MANIA AND HYPOMANIA

- Mood elevated or irritable
- Increased energy/activity
- Grandiosity/inflated sense of importance
- Decreased sleep
- Increased speech or pressured speech
- Flight of ideas or sense of racing thoughts
- Distractibility
- Increase in goal-directed behavior or agitation
- Risky behaviors

For a diagnosis of hypomania, the symptoms must have been present for at least 4 days, and the patient must not have marked impairment in functioning or require hospitalization.

For a diagnosis of mania, the symptoms must have been present for 1 week or the patient must have been hospitalized for any duration. Also, the symptoms must cause marked impairment in functioning or require hospitalization. Psychosis also fulfills this requirement.

**15. False**

One does not have to have had a major depressive episode to be diagnosed with bipolar I disorder, only a manic episode.

**16. True**

To be diagnosed with bipolar II disorder, the patient must have had a hypomanic episode and a major depressive episode. A manic episode indicates that the patient has bipolar I disorder, not bipolar II disorder.

**17. D**

To meet criteria for panic disorder, a patient must have—in addition to recurrent, unexpected panic attacks—fear of an attack or the consequences of an attack, or a maladaptive change in behavior to avoid an attack, for at least 1 month.

Panic attacks can occur in the setting of other psychiatric disorders. In these patients, the attacks may not necessarily represent a comorbid panic disorder. Rather, they may constitute a specifier for the primary diagnosis, such as social anxiety disorder with panic attacks.

**18. A**

This patient has disruptive mood dysregulation disorder, which was a new diagnosis in the DSM-5. The core feature of this diagnosis is chronic and severe irritability. It is characterized by persistent, recurrent temper outbursts that are grossly out of proportion to the situation. The temper outbursts must occur an average of three times a week over the course of a year in at least two settings. The age at onset is younger than 10 years, but the diagnosis should not be made in children younger than age 6 years. Also, the diagnosis of disruptive mood dysregulation disorder should not be made initially after age 18 years. A patient with disruptive mood dysregulation disorder may also be diagnosed with anxiety, depression, or ADHD if they meet criteria. This diagnosis cannot coexist with that of oppositional defiant disorder (ODD), bipolar disorder, or intermittent explosive disorder. Children with disruptive mood dysregulation disorder are at risk for depression and anxiety, and the diagnosis is listed among the depressive disorders in DSM-5 and DSM-5-TR.

ODD is characterized by irritability, defiant/argumentative behavior, or vindictiveness. Like patients with disruptive mood dysregulation disorder, patients with ODD have irritability and outbursts; however, in patients with ODD, these outbursts are less frequent and less severe.

The absence of hypomania in disruptive mood dysregulation disorder aids in its differentiation from bipolar II disorder. It is hoped that the ability to diagnose disruptive mood dysregulation disorder will prevent overdiagnosis of bipolar disorder.

A patient with intermittent explosive disorder is unable to control outbursts or aggressive behaviors triggered by a minimal stimulus. Patients with intermittent explosive disorder lack the enduring negative mood symptoms found in patients with disruptive mood dysregulation disorder.

Conduct disorder is characterized by premeditated aggression and destruction. Destruction in disruptive mood dysregulation disorder and in intermittent explosive disorder is not premeditated or goal oriented.

**19. A**

Aggression toward animals or individuals, theft, destruction of property, and deceitfulness help differentiate conduct disorder from ODD. Also, mood dysregulation is characteristic of ODD, not conduct disorder. The absence of mood symptoms in conduct disorder also helps differentiate it from disruptive mood dysregulation disorder.

**20. E**

This patient has somatic symptom disorder, which is characterized by excessive concern about somatic symptoms lasting at least 6 months.

The DSM-5 and DSM-5-TR refer to somatoform disorders as somatic symptom and related disorders. The number of disorders has decreased compared with DSM-IV. Hypochondriasis, pain disorder, somatization disorder, and undifferentiated somatoform disorder are not included in DSM-5 or DSM-5-TR. Factitious disorder and functional neurological symptom disorder (conversion disorder) are included among somatic symptom and related disorders. The focus of these disorders is the distress or impairment caused by somatic symptoms. Less emphasis is placed on the lack of medical explanation for the symptoms.

Most of the patients who previously were diagnosed with hypochondriasis will now meet criteria for somatic symptom disorder. Some of the patients who would have been diagnosed with hypochondriasis will now be diagnosed with illness anxiety disorder. These patients have excessive anxiety about their health but do not have somatic symptoms or have only mild symptoms. Patients with more severe somatic symptoms are diagnosed with somatic symptom disorder.

In functional neurologic symptom disorder (conversion disorder), the patient has neurologic symptoms that cannot be explained.

Patients with body dysmorphic disorder are focused on a perceived defect in their appearance. This is included in the section with obsessive–compulsive and related disorders.

Factitious disorder is diagnosed when symptoms are consciously feigned, even if there is no obvious reward.

**21. False**

The criteria for anorexia are restricted intake to the point that the patient has a significantly low weight, fear of gaining weight or behavior that interferes with weight gain, and disturbance in body image. In the DSM-5 and DSM-5-TR, amenorrhea is not required for the diagnosis.

There was also a change in the criteria for bulimia nervosa in the DSM-5 and DSM-5-TR. The minimum frequency of binge-eating and compensatory behavior was reduced from twice weekly to once weekly for 3 months.

**22. False**

The presence of recurring, distressing dreams or memories can be used to meet criteria for intrusion symptoms, which occur in PTSD. Alternatively, physiologic reactions or psychological distress on exposure to reminders of the trauma can be used to meet criteria for intrusion symptoms. Flashbacks, which are a type of dissociative reaction, are *not* required to meet criteria for PTSD.

**23. D**

This is dissociative amnesia, which is characterized by inability to recall information about one's life, particularly an event that was stressful. Dissociative amnesia can be a stand-alone diagnosis, or it can be present as a part of other disorders—for example, in dissociative identity disorder, which is defined as the presence of at least two personality states.

Depersonalization is the feeling of being detached from one's self, such as feeling as if one is observing one's self from outside one's body.

Derealization is characterized by feeling detached from one's environment or feeling that one's surroundings are distorted or dream-like.

Depersonalization and derealization can occur in depersonalization/derealization disorder, or they can occur in acute stress disorder or PTSD (but are not necessary for diagnosis of those disorders). Acute stress disorder is similar to PTSD, but the duration of the symptoms is 3 days to 1 month. To meet criteria for PTSD, symptoms must last for at least 1 month.

**24. B**

A child must be at least 5 years old (chronologically or developmentally) to be diagnosed with enuresis. Encopresis can be diagnosed at age 4 years.

**25. False**

A paraphilia, in itself, is not necessarily a mental disorder, according to the DSM-5 and DSM-5-TR. If it causes distress or impairment or involves a nonconsenting person, then it is a mental disorder.

**26. C**

The major use of electroconvulsive therapy (ECT) is for depression. A generalized seizure is needed for ECT to have an antidepressive effect. Other uses are for mania, psychosis, and catatonia.

Lithium increases the risk for delirium after the procedure and the risk for prolonged seizure activity.

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Bupropion and clozapine also lower the seizure threshold. Benzodiazepines increase the seizure threshold.

Headache and muscle soreness are the most common side effects of ECT. Postictal confusion is a concern. Older age, cognitive deficits, and neurologic disease are risk factors for postictal confusion, as are increased ECT intensity, bilateral treatment, greater number of treatments, and more frequent treatments. The impact of ECT on memory is also a concern.

**27. B**

This patient has obsessive–compulsive personality disorder, which is characterized by inflexibility and perfectionism at the expense of productivity.

OCD is characterized by obsessions and/or compulsions, which do not occur in obsessive–compulsive personality disorder.

Histrionic personality disorder is characterized by increased emotionality and the desire for attention.

Narcissism is discussed below.

**28. True**

OCD is characterized by obsessions and/or compulsions that consume time and cause distress. Obsessions are recurrent, distressing, intrusive thoughts. The patient may try to negate them by performing repetitive behaviors (compulsions) with rigid requirements. The first-line pharmacologic treatment for OCD is SSRIs. Cognitive–behavioral therapy is the most effective form of psychotherapy for OCD.

Obsessions and compulsions are not required for the diagnosis of obsessive–compulsive personality disorder. The essential feature of obsessive–compulsive personality disorder is a preoccupation with orderliness and control at the expense of flexibility and efficiency. Some characteristics of this disorder are preoccupation with rules and schedules, perfectionism that interferes with task completion, extreme devotion to work, inflexibility regarding morals or values, inability to discard useless items, reluctance to delegate tasks, aversion to spending money, and rigidity or stubbornness.

In the DSM-5 and DSM-5-TR, obsessive–compulsive personality disorder is not included in the chapter about OCD and related disorders but, rather, in the chapter about personality disorders. The chapter about OCD and related disorders includes the diagnoses of OCD, body dysmorphic disorder, hoarding disorder, and excoriation (skin-picking) disorder. Trichotillomania (hair-pulling) disorder was moved from the chapter on impulse-control disorder in DSM-IV to the chapter on OCD and related disorders in DSM-5 and DSM-5-TR.

**29. C**

Patients with cluster C personality disorders (avoidant, dependent, and obsessive–compulsive personality disorders) tend to be anxious.

Patients with cluster A personality disorders (paranoid, schizoid, and schizotypal personality disorders) tend to be eccentric.

Patients with cluster B personality disorders (antisocial, borderline, histrionic, and narcissistic personality disorders) tend to be dramatic and emotional.

**30. C**

Patients with schizoid personality disorder do not care about forming relationships, choose to be alone, and seem emotionally cold.

Patients with avoidant personality disorder feel inferior and avoid new relationships and situations because of fear of rejection.

Patients with narcissistic personality disorder have an exaggerated sense of worth, need admiration, and lack empathy.

Patients with schizotypal personality disorder have unusual beliefs and behaviors and do not have close friends.

**31. C**

Patients with borderline personality disorder have mood instability, a fear of abandonment, and unstable relationships. They are impulsive and may demonstrate suicidal behaviors or self-mutilate. They have disturbance of identity, chronic feelings of emptiness, trouble with anger, and may have transient stress-related paranoia or dissociative symptoms. Dialectical behavior therapy has been used in patients with borderline personality disorder.

Deceitfulness and lack of remorse are features of antisocial personality disorder.

Arrogance is a feature of narcissistic personality disorder.

**32. B**

This is intellectualization. Rather than addressing his grief, he is distancing himself from the problem through his research.

Denial is a primitive defense mechanism. If he were using denial as a psychological defense, he would not be able to accept or believe that he had a brain tumor.

Rationalization is an unconscious defense mechanism in which the individual attempts to provide a logical justification for an unacceptable behavior or feeling. The result is giving a false, more acceptable reason for one's behavior.

Undoing is a primitive defense mechanism in which an action is performed to counteract a prior behavior for which one feels guilty.

**33. True**

The Tarasoff rule indicates that there is a duty to protect a person from injury if a psychiatric patient has indicated that they plan to harm the person. In such a case, confidentiality may be breached.

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**34. C**

Selegiline is a monoamine oxidase B (MAO-B) inhibitor. However, at higher doses, it can also inhibit MAO-A. Tranylcypromine and phenelzine are MAO inhibitors that inhibit MAO-A and MAO-B.

The combination of a MAO-A inhibitor and a serotonergic medication can result in serotonin syndrome. Serotonin syndrome is associated with confusion, tachycardia, hyperreflexia, clonus, myoclonus, and shivering. It can be treated with cyproheptadine or benzodiazepines.

Patients on MAO inhibitors must also avoid foods with tyramine, which can lead to hypertensive crisis.

**35. C**

Paroxetine has a short half-life, which results in an increased risk for withdrawal symptoms. Abrupt discontinuation of an SSRI can cause discontinuation syndrome, which is characterized by dizziness, anxiety, nausea, headache, and irritability. Paroxetine withdrawal effects may also be related to the fact that it inhibits its own metabolism. When the drug is withdrawn, its rate of decline in the body can become faster because this self-inhibition ends.

Fluoxetine has a long half-life, as does its major metabolite. Therefore, there is a low risk for discontinuation syndrome. However, one must wait a long time (at least 5 weeks) between discontinuing fluoxetine and starting an MAO inhibitor.[3]

**36. D**

Bupropion (Wellbutrin) is a norepinephrine–dopamine reuptake inhibitor. It does not have serotonergic activity. Its structure is similar to that of a stimulant. As a result, a patient taking bupropion who undergoes urine drug screening can test positive for amphetamines, depending on the screen used.

**37. C**

Bupropion lowers the seizure threshold and should not be used in patients with bulimia. It is much less likely than SSRIs to have sexual side effects. It has been used to treat ADHD and for smoking cessation.

**38. D**

Trazodone is a serotonin antagonist and reuptake inhibitor (SARI). It is an antagonist to the serotonin 5-$HT_2$ receptor. Trazodone, mirtazapine, nefazodone, and bupropion are considered atypical antidepressants.

Mirtazapine (Remeron), which has a tetracyclic structure, is a noradrenergic and specific serotonergic antidepressant. It increases serotonin and norepinephrine release by blocking $\alpha_2$ adrenergic presynaptic receptors. It does not inhibit serotonin reuptake. Mirtazapine blocks 5-$HT_{2A}$, 5-$HT_{2C}$, and 5-$HT_3$ serotonin receptors and the $H_1$ histamine receptor.[3] It causes sedation, so it is used to treat patients with concomitant insomnia. It also causes weight gain.

Viloxazine and atomoxetine, which are used to treat ADHD, are serotonin–norepinephrine reuptake inhibitors (SNRIs). SNRIs and TCAs, such as imipramine, bind the serotonin transporter (SERT) and the norepinephrine transporter (NET).

Duloxetine, venlafaxine, and desvenlafaxine are also SNRIs; they are used to treat depression. In addition, duloxetine has been used to treat diabetic peripheral neuropathy. It can cause nausea.

Phenelzine, tranylcypromine, and selegiline are MAO inhibitors.

**39. E**

TCAs tend to cause sedation and weight gain because of their antihistamine effect. TCAs include amitriptyline, nortriptyline, imipramine, desipramine, clomipramine, amoxapine, and doxepin. TCAs have anticholinergic side effects, such as dry mouth and urinary retention. TCAs can cause cardiac arrhythmias and can be lethal in overdose (see Box 26.4).

### *Box 26.4* MECHANISMS OF ACTION OF TRICYCLIC ANTIDEPRESSANTS

- Serotonin reuptake inhibition
- Norepinephrine reuptake inhibition
- Anticholinergic effects (central and peripheral)
- Antihistamine effects (central and peripheral)
- Peripheral $\alpha_1$ antagonism
- Fast sodium channel blockade

**40. D**

Trazodone rarely can cause priapism. It is indicated for major depression and is used for insomnia because it is sedating.

Trazodone can cause a false-positive test for amphetamines on urine drug screening.

Nefazodone blocks the 5-$HT_{2A}$ receptor, similar to trazodone and mirtazapine. It can cause sedation and hepatotoxicity.

**41. B**

There is an increased risk for cerebrovascular events and death in elderly patients taking antipsychotics.

Neuroleptics/conventional antipsychotics treat psychosis by blocking $D_2$ receptors in the mesolimbic pathway. Cariprazine, which is a newer antipsychotic, has a greater affinity for $D_3$ receptor than $D_2$ receptor at low doses.[3]

Blockage of $D_2$ receptors in the tuberoinfundibular pathway can cause hyperprolactinemia, and blockage of $D_2$ receptors in the nigrostriatal pathway can cause extrapyramidal symptoms. Atypical antipsychotics (except

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risperidone) tend to have less risk for extrapyramidal side effects and hyperprolactinemia than conventional antipsychotics.

Most atypical antipsychotics (also referred to as second-generation antipsychotics) are serotonin–dopamine antagonists; they antagonize the 5-HT$_{2A}$ receptor as well as the D$_2$ receptor. Atypical antipsychotics also act more specifically on the mesolimbic rather than striatal pathways. An antipsychotic that is a partial agonist at the 5-HT$_{1A}$ receptor or at the D$_2$ receptor is also called atypical.

Antipsychotics also act at multiple other receptors. Some have anticholinergic side effects, such as dry mouth, urinary retention, constipation, and blurred vision. The neuroleptics with potent anticholinergic effects tend to have less extrapyramidal symptoms. $\alpha$-Adrenergic blockade can cause orthostatic hypotension and drowsiness. Blockage of histamine H$_1$ receptors causes sedation.

Low-potency neuroleptics tend to have more anticholinergic, antihistaminic, and $\alpha_1$-antagonist properties than high-potency neuroleptics; therefore, they tend to be more sedating and to cause more weight gain. They also cause orthostatic hypotension more frequently. Chlorpromazine (Thorazine) and thioridazine (Mellaril) are low-potency antipsychotics. Retinitis pigmentosa is a possible side effect of thioridazine. Haloperidol and pimozide (Orap) are high-potency neuroleptics.

High-potency neuroleptics are associated with the greatest risk for neuroleptic malignant syndrome (NMS), which is due to dopamine depletion. However, NMS can occur with any antidopaminergic medication or with sudden discontinuation of a dopaminergic medication. NMS is associated with fever, rigidity, mental status changes, and autonomic instability. Rhabdomyolysis can occur. In addition to supportive care, benzodiazepines, dopamine agonists, and dantrolene have been used for treatment of NMS.

**42. A**

As discussed previously, atypical antipsychotics may be antagonists at the 5-HT$_{2A}$ receptor, partial agonists at the D$_2$ receptor, or partial agonists at the 5-HT$_{1A}$ receptor. Most are antagonists of the 5-HT$_{2A}$ receptor. Aripiprazole (Abilify) is a partial agonist at the D$_2$ and 5-HT$_{1A}$ receptors, as well as an antagonist of the 5-HT$_{2A}$ receptor. Other dopamine receptor partial agonists are brexpiprazole and cariprazine.

Aripiprazole has a relatively lower risk for extrapyramidal symptoms than most antipsychotics. Antagonism of the 5-HT$_{2A}$ receptor may improve negative symptoms of schizophrenia. Aripiprazole does not have significant anticholinergic activity but does have antihistaminergic and anti-adrenergic activity. There is a relatively low risk of dyslipidemia. There is a risk for impulse control disorders with aripiprazole.

Aripiprazole is approved for schizophrenia, acute mania/mixed mania, bipolar disorder, autism-related irritability, Tourette syndrome, and acute agitation associated with schizophrenia and bipolar disorder. It is also approved as adjunctive therapy for depression.[3]

In addition to antagonizing multiple receptors, including the D$_2$ and 5-HT$_{2A}$ receptors, Ziprasidone (Geodon) also inhibits norepinephrine and serotonin reuptake. There is a lower risk compared with other antipsychotics for weight gain, insulin resistance, and dyslipidemia. However, ziprasidone does prolong the QTc interval.

Valbenazine and deutetrabenazine are vesicular monoamine transporter type 2 inhibitors. They are used to treat tardive dyskinesia. They reduce uptake of dopamine (and other neurotransmitters, such as serotonin and norepinephrine) into presynaptic vesicles, leading to less neurotransmitter release.

(Quetiapine and olanzapine are discussed in Question 44.)

**43. A**

Iloperidone, lurasidone, and paliperidone are all atypical antipsychotics; they are antagonists at the D$_2$ and 5-HT$_{2A}$ receptors.

Iloperidone (Fanapt) demonstrates potent $\alpha_1$ antagonism. It has a low metabolic risk and a low risk for extrapyramidal symptoms, but it does cause dose-dependent lengthening of the QT interval. It is metabolized by CYP2D6 and CYP3A4.

Lurasidone (Latuda) is a strong antagonist of the 5-HT$_7$ receptor. It does not significantly increase glucose or lipids and does not affect the QT interval as much as many other antipsychotics do.

Paliperidone (Invega) is an active metabolite of risperidone; however, it is not metabolized in the liver.

**44. C**

Clozapine, which is a weak D$_2$ antagonist and a strong 5-HT$_{2A}$ antagonist, can be used for psychotic patients who are at increased risk of EPSs, including patients with Parkinson disease who develop psychosis. It has a lower risk for EPSs and tardive dyskinesia than most antipsychotics. It is one of the most effective treatments for psychosis in patients for whom other antipsychotic medications have failed. However, it lowers the seizure threshold and can cause agranulocytosis. It does not increase prolactin. Relative to other atypical antipsychotics, it has more anticholinergic side effects and tends to cause more weight gain. Clozapine has black box warnings for agranulocytosis, seizures, myocarditis, cardiovascular and respiratory effects (e.g., orthostatic hypotension), and increased mortality in elderly patients with dementia-related psychosis. Constipation is also a concern.[4]

Olanzapine (Zyprexa), which is an atypical antipsychotic (a serotonin–dopamine antagonist), is structurally similar to clozapine; however, it has less risk for agranulocytosis and seizures. Similar to clozapine, olanzapine has less risk for EPSs than most antipsychotics.

Both clozapine and olanzapine carry a very high risk for weight gain.

Quetiapine (Seroquel), which has structural similarities to olanzapine and clozapine, also has a low risk for EPSs. Quetiapine is a serotonin–dopamine antagonist, but its receptor binding properties depend on the dose. The immediate-release formulation blocks $H_1$ receptors quickly, causing sedation. In order to occupy sufficient $D_2$ receptors for a full day without high dosing, twice-daily doses of the immediate formulation of quetiapine or once-daily doses of the extended-release formulation may be needed. Quetiapine is unlikely to increase prolactin levels.

CYP1A2, which metabolizes olanzapine and clozapine, is induced by smoking. Therefore, smokers may need higher doses of these medications. Fluvoxamine inhibits CYP1A2 and can raise the level of clozapine, which can increase the risk for seizures.

**45. D**

Lithium can cause weight gain. It can also cause diarrhea, tremor, edema, acne, and nephrogenic diabetes insipidus. It can affect the thyroid gland. Lithium toxicity can result in seizures and arrhythmias. The cardiac effects of lithium resemble those of hypokalemia on the ECG (i.e., T-wave flattening or inversion). Lithium can be teratogenic.

Most diuretics and angiotensin-conversion enzyme inhibitors increase the risk of lithium toxicity. An encephalopathic syndrome has been reported in patients who received the combination of lithium and haloperidol. Dehydration can also lead to increased levels of lithium, which can result in toxicity.

**46. A**

Cocaine, amphetamines, anticholinergics, antihistamines, sympathomimetics, thyroid hormone, and theophylline can produce tachycardia. Decreased bowel sounds are characteristic of anticholinergic medications. This patient most likely ingested amitriptyline, which is a TCA. TCAs produce anticholinergic side effects, such as mydriasis and dry mucous membranes, in addition to tachycardia and absent bowel sounds. Sodium bicarbonate is sometimes used in the treatment of TCA poisoning.

Fentanyl and meperidine are opioids. Opiate toxicity causes somnolence, pupillary miosis, respiratory depression, and decreased bowel sounds. Opiates can also cause flash pulmonary edema. Meperidine also can cause seizures. Opioid overdose is treated with naloxone, which is an opioid receptor antagonist.

**47. D**

Selegiline, which is a MAO-B inhibitor, is the most likely to cause mania. Cholinesterase inhibitors, β-blockers, and isotretinoin are more likely to cause depression.

**48. C**

Carbamazepine, oxcarbazepine, lithium, and valproic acid are mood stabilizers. Some atypical antipsychotics are approved for treatment of bipolar disorder as well. Antidepressants, such as TCAs, can cause mania in patients with bipolar disorder when used in monotherapy.

**49. A**

Cognitive–behavioral therapy is used in multiple conditions, including depression, anxiety disorders, obsessive–compulsive disorders, PTSD, and eating disorders.

The nonpharmacologic therapy of choice for autism is applied behavior analysis.

**50. D**

Brexanolone, levomilnacipran, vilazodone, and vortioxetine are antidepressants.

Vilazodone was the first serotonin partial agonist reuptake inhibitor (SPARI). It is a partial agonist at $5\text{-HT}_{1A}$ and a serotonin reuptake inhibitor. It has less risk for sexual dysfunction than other antidepressants that block serotonin reuptake. Patients on vilazodone should avoid MAO inhibitors. There is a risk for increased seizures.

Brexanolone was the first antidepressant that demonstrated positive allosteric modulation of the benzodiazepine-insensitive γ-aminobutyric acid A ($\text{GABA}_A$) receptor. It was also the first medication approved for postpartum depression, but it is given intravenously. Zuranolone, which is a neuroactive steroid $\text{GABA}_A$ receptor positive allosteric modulator, was the first oral medication approved for postpartum depression.

Levomilnacipran is an serotonin-norepinephrine reuptake inhibitor (SNRI). Other SNRIs are duloxetine, venlafaxine, and desvenlafaxine. Levomilnacipran has a risk for seizures and has noradrenergic properties. Uncontrolled angle-closure glaucoma and MAO inhibitors are contraindications.

Vortioxetine has multimodal mechanisms of action. It increases the release of multiple neurotransmitters, such as serotonin, norepinephrine, dopamine, glutamate, acetylcholine, and histamine. It reduces the release of GABA. It blocks the serotonin transporter, which blocks serotonin reuptake. It binds to G protein-linked receptors.

Pimavanserin is an atypical antipsychotic used to treat hallucinations and delusions associated with psychosis in Parkinson disease. Antipsychotics, particularly those that reduce dopaminergic activity, worsen motor symptoms in Parkinson disease. Pimavanserin is a $5\text{-HT}_{2A/2C}$ antagonist/inverse agonist. It is not associated with weight gain. It can cause peripheral edema, confusion, nausea, and QT prolongation.[3] (See Supplementary Tables 26.2 and 26.3.)

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## SUPPLEMENTARY INFORMATION

### *Table 26.2* CHARACTERISTIC FEATURES OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS

| SSRI | CHARACTERISTIC FEATURES |
|---|---|
| Citalopram | Risk for QTc prolongation at higher doses, mild antihistaminergic activity |
| Escitalopram | Low risk of CYP-mediated drug interactions, no antihistaminergic activity |
| Fluoxetine | Long half-life, 5-HT$_{2C}$ antagonist, tends to be activating |
| Fluvoxamine | Sigma-1 receptor binding |
| Paroxetine | Short half-life, high risk for withdrawal reaction, muscarinic anticholinergic activity and norepinephrine transporter inhibition |
| Sertraline | Dopamine transporter inhibition and sigma-1 receptor binding, can be activating |

SSRI, selective serotonin reuptake inhibitor.

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### *Table 26.3* CHARACTERISTIC FEATURES OF ANTIPSYCHOTICS[a]

| ANTIPSYCHOTIC | CHARACTERISTIC FEATURES |
|---|---|
| Aripiprazole (Abilify) | Partial agonist at the D$_2$ and 5-HT$_{1A}$ receptors |
| Asenapine (Saphris) | Has a sublingual formulation. Its chemical structure is related to mirtazapine. |
| Brexipiprazole (Rexulti) | Similar to aripiprazole. Partial agonist at D$_2$ and 5-HT$_{1A}$ receptors. More binding to serotonin receptors than aripiprazole. |
| Cariprazine (Vraylar) | Dopamine receptor partial agonist. Greater affinity for D$_3$ receptor than D$_2$ receptor at low doses. Long-lasting metabolite. |
| Clozapine (Clozaril) | Risk for agranulocytosis, seizures, myocarditis, significant constipation; weight gain; anticholinergic side effects |
| Iloperidone (Fanapt) | Dose-related QT prolongation, potent $\alpha_1$ antagonism |
| Lumateperone (Caplyta) | Serotonin-dopamine antagonist |
| Lurasidone (Latuda) | Antagonist at 5-HT$_7$ receptor, low risk of weight gain, low risk of QT prolongation |
| Olanzapine (Zyprexa) | Strong potency at H$_1$ and 5-HT$_{2A}$ receptors, weight gain |
| Paliperidone (Invega) | Active metabolite of risperidone, not hepatically metabolized |
| Pimavanserin (Nuplazid) | 5-HT$_{2A/2C}$ antagonist/inverse agonist. Used to treat hallucinations in patients with psychosis associated with Parkinson disease. |
| Quetiapine (Seroquel) | Serotonin–dopamine antagonist. Binding properties depend on the dose. Used for schizophrenia and bipolar disorder. Less motor symptoms than conventional antipsychotics. |
| Risperidone (Risperdal) | At higher doses can cause extrapyramidal symptoms, similar to conventional antipsychotics |
| Ziprasidone (Geodon) | Inhibits norepinephrine and serotonin reuptake; weight gain and dyslipidemia are not commonly an issue. Prolongs the QT interval. Risk for drug reaction with eosinophilia and systemic systems (DRESS). |

[a] There is an increased risk for cerebrovascular events and death in elderly patients taking antipsychotics.

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# 27.

# SLEEP DISORDERS

## QUESTIONS

1. **A 20-year-old patient presents with sleepiness. He is afraid he is going to lose his job because he falls asleep at work. When he awakens in the morning, he feels refreshed, but for a brief period he feels as if he cannot move. Also, he has been falling when he laughs. Which abnormality of the cerebrospinal fluid (CSF) is most closely associated with this condition?**
   A. Increased protein
   B. Decreased glucose
   C. Decreased orexin
   D. Increased hypocretin
   E. Decreased serotonin

2. **Which of the following statements is *false*?**
   A. Infants spend a greater amount of time asleep than adults do, and they spend a greater portion of the time in rapid-eye-movement (REM) sleep.
   B. Sleep efficiency decreases with age.
   C. The elderly spend more time in stage N3 sleep than younger adults do.
   D. Neonates enter sleep through the REM stage.

3. **Which of the following symptoms is *least* suggestive of obstructive sleep apnea (OSA)?**
   A. Arousals due to choking
   B. Awakening diaphoretic
   C. Morning headaches
   D. Morning vomiting

4. **Which of the following statements is *false* regarding children with obstructive sleep apnea (OSA)?**
   A. A sleep study should be done for OSA only if the patient's teacher or parent reports that the patient appears sleepy.
   B. Children with OSA are more likely to have partial obstruction than complete obstruction.
   C. Adenotonsillar enlargement frequently is found in children with OSA.
   D. Pediatric criteria for OSA require fewer respiratory disturbances per hour than the adult criteria do.

5. **A mother brings her 6-year-old son to the clinic because of events that happen at night. The patient wakes up approximately 2 hours after going to sleep and screams. He appears scared. He is tachycardic and diaphoretic. His mother cannot console him. In the morning, he has no memory of the event. What is the most likely diagnosis?**
   A. Sleep terror disorder
   B. Nightmares
   C. REM sleep behavior disorder (RBD)
   D. Restless leg syndrome (RLS)

6. **Which of the following statements is *false*?**
   A. Excessive daytime sleepiness is suspected when a person sleeps in an atypical setting or falls asleep unintentionally.
   B. Alcohol and sleep deprivation increase snoring.
   C. The STOP-BANG questions are a method of screening for OSA.
   D. Home sleep testing (HST) should be considered for all patients who are being evaluated for classic polysomnograms (PSGs).
   E. The Epworth Sleepiness Scale is a tool used to assess for excessive daytime sleepiness.

7. **True or false?**
   Patients with narcolepsy are instructed to avoid naps in the daytime to improve sleep quality at night.

8. **A 60-year-old man is brought to the office by his wife. The wife reports that her husband has been awakening from sleep and tackling her and the furniture. Afterward, he tells her he has been dreaming of football. What is the most likely diagnosis?**
   A. Confusional arousals
   B. REM sleep behavior disorder
   C. Sleepwalking
   D. Sleep terrors

9. **A 30-year-old patient presents with difficulty sleeping due to an uncomfortable feeling in her legs. The feeling makes her want to move her legs and is worse in the evening. Which of the following laboratory tests should be performed first?**
   A. Vitamin $B_{12}$ level
   B. Ferritin level
   C. Folate level
   D. Hemoglobin electrophoresis

10. **Which of the following medications is used *least* often to treat restless leg syndrome?**
    A. Benzodiazepines
    B. Calcium channel $\alpha_2\delta$ ligands
    C. Dopaminergic agents
    D. Selective serotonin reuptake inhibitors (SSRIs)

11. **Which of the following statements is *false*?**
    A. Paradoxical insomnia occurs when patients have slept but think they have been awake.
    B. In order to diagnose insomnia, there should be an impact on daytime activities.

C. Circadian rhythm disorders may be mistaken for insomnia or excessive sleepiness.
D. With chronic sleep deprivation, one's perception of sleepiness is impaired.
E. A PSG should not be ordered for OSA unless there is at least mild snoring.

**12. Which of the following is *not* a risk factor for somnambulism (sleepwalking)?**
A. Sleep deprivation
B. Zolpidem
C. Stress
D. Genetic susceptibility
E. Clonazepam

**13. A 16-year-old boy is brought to clinic because of sleepiness during the day. He gets in bed at 11 p.m. but says he does not feel sleepy until 2 a.m. School starts at 7:30 a.m. He has been chastised for falling asleep in school. On weekends, he sleeps until 4 p.m. He says he sleeps well once he falls asleep. He denies caffeine intake in the afternoon. Which of the following diagnoses should be considered?**
A. Advanced sleep phase disorder
B. Delayed sleep phase disorder
C. Irregular sleep–wake rhythm disorder

**14. What is the mechanism of action of ramelteon?**
A. Benzodiazepine receptor agonist
B. Selective histamine $H_1$ receptor antagonist
C. Selective melatonin receptor agonist
D. Glutamate agonist

**15. Which of the following medications does *not* increase slow-wave sleep?**
A. Zolpidem
B. Gabapentin
C. Mirtazapine
D. Pregabalin
E. Trazodone

**16. Which of the following medications is most helpful in treating sleep maintenance insomnia?**
A. Doxepin
B. Ramelteon
C. Zaleplon
D. Zolpidem oral spray

**17. Which of the following is the best description of hypersomnia in an adult?**
A. Sleeping more than 10 hours per night
B. Sleeping more than 12 hours per night
C. Excessive daytime sleepiness and difficulty maintaining alertness when awake
D. Feeling fatigued

**18. Which of the following is *not* characteristic of REM sleep?**
A. Low muscle tone on submental electromyography
B. Sawtooth waves
C. Low-amplitude, mixed-frequency electroencephalography (EEG)
D. Increase in epileptiform activity
E. Irregular breathing

**19. Which of the following is *least* likely to cause sleep-onset REM?**
A. Circadian rhythm disorder
B. Deprivation of REM sleep
C. Withdrawal of medications that suppress REM
D. Fluoxetine

**20. Which of the following statements is *false*?**
A. Central apnea is the absence of effort to breathe.
B. In exploding head syndrome, one hears an explosion sound as one falls asleep.
C. Sleep drunkenness is unsteadiness caused by severe sleep deprivation.
D. Hypnic headaches can occur outside of REM sleep.

**21. Which of the following statements is *false*?**
A. Tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and SSRIs can cause behavior similar to that seen with RBD.
B. Cognitive–behavioral therapy is not helpful in treating insomnia.
C. Carefully timed administration of bright light and melatonin can be used to treat circadian rhythm disturbances.
D. Treatment of RLS with dopamine agonists can result in worsening of symptoms earlier in the day or symptoms in the morning.

**22. Which of the following statements is *false*?**
A. Sleep-disordered breathing is a risk factor for stroke.
B. A significant number of patients with resistant hypertension have OSA.
C. Sleep disturbance occurs in the majority of patients with Huntington disease.
D. Patients with cluster headache do not have an increased risk of OSA.

**23. To be diagnosed with enuresis, a child should be at least _____ years old.**
A. 3
B. 5
C. 7
D. 8

**24. Which of the following statements regarding the comparison of nocturnal frontal lobe seizures and non-REM parasomnias is *false*?**
A. Seizures are more stereotyped.
B. Seizures may occur many times in the night.
C. Seizures tend to be shorter.
D. Non-REM parasomnias usually occur during the few hours before the patient awakens.

**25. Which of the following is *not* a non-REM sleep disorder?**

A. Confusional arousals
B. Sleepwalking
C. Sleep terrors
D. Recurrent isolated sleep paralysis

**26. Which of the following symptoms is most helpful in differentiating sleep terrors from other parasomnias?**

A. Sympathetic activation
B. Confusion after the event
C. Duration

**27. Where are circadian rhythms generated?**

A. Pulvinar nucleus of the thalamus
B. Anterior nucleus of the thalamus
C. Suprachiasmatic nucleus of the hypothalamus
D. Arcuate nucleus of the hypothalamus

**28. Why do patients with Alzheimer disease have sleep–wake disturbances?**

A. There is damage to cholinergic neurons in the suprachiasmatic nucleus and the ventrolateral preoptic nucleus.
B. There is damage to the ventral arcuate nucleus and the pre-Bötzinger complex of the medulla.
C. There is damage to the sublaterodorsal tegmental nucleus.

**29. During sleep, neurons in the arousal system are inhibited by which neurotransmitter?**

A. Dopamine
B. $\gamma$-Aminobutyric acid (GABA)
C. Glycine
D. Histamine
E. Serotonin

**30. Which of the following inhibit(s) the arousal system during sleep?**

A. Parabrachial nucleus
B. Ventral periaqueductal gray matter
C. Ventrolateral preoptic nuclei (VLPO) and median preoptic nuclei (MNPO)

**31. Where are the neurons that generate REM sleep?**

A. Dorsal raphe
B. Locus coeruleus
C. Subcoeruleus area/sublaterodorsal nucleus and precoeruleus region of the pons
D. Tuberomammillary nucleus

**32. Which areas of the brain are responsible for stopping REM, acting as the REM-off center?**

A. Ventrolateral periaqueductal gray matter and lateral pontine tegmentum (vlPAG/LPT)
B. Ventrolateral preoptic nuclei (VLPO)
C. Laterodorsal tegmental nuclei (LDT)
D. Pedunculopontine tegmental nuclei (PPT)

**33. Sleep diaries are most helpful for diagnosing which of the following conditions?**

A. Circadian rhythm disorders
B. Obstructive sleep apnea
C. Restless leg syndrome
D. REM sleep behavior disorder

**34. Actigraphy is most helpful for diagnosing which of the following conditions?**

A. Circadian rhythm disorders
B. Obstructive sleep apnea
C. REM sleep behavior disorder
D. Restless leg syndrome

**35. Which of the following statements is *false*?**

A. The Multiple Sleep Latency Test (MSLT) is helpful in any age group.
B. A mean sleep latency of less than 8 minutes plus at least two sleep-onset REM events is consistent with the diagnosis of narcolepsy.
C. A polysomnogram (PSG) is done the night before an MSLT; however, a PSG is not required the night before a Maintenance of Wakefulness Test (MWT).

**36. The parents of a 15-year-old boy report that for the past week he has awakened only to eat, and during that time he eats an extremely large amount. On further questioning, they state that this behavior has occurred on two other occasions in the past year. During the episodes, he is confused and apathetic. When the episodes are over, he returns to normal. Which of the following is the most likely etiology?**

A. Immunoglobulin-like cell adhesion molecule 5 (IgLON5) autoantibodies
B. Kleine–Levin syndrome
C. Narcolepsy
D. *PHOX2B* mutation
E. Rapid-onset obesity with hypoventilation, hypothalamic dysfunction, autonomic dysregulation syndrome (ROHHAD)

# SLEEP DISORDERS

## ANSWERS

### 1. C

This patient most likely has narcolepsy type 1, which is associated with low levels of hypocretin/orexin in the cerebrospinal fluid (CSF).

Narcolepsy is accompanied by the following symptoms: excessive daytime sleepiness, cataplexy, hypnagogic or hypnopompic hallucinations, and sleep paralysis. Patients do not have to have all of the symptoms. To meet criteria, the duration of excessive daytime sleepiness should be at least 3 months. Patients with narcolepsy can have disrupted sleep at night, including difficulty going to sleep. Most patients who have narcolepsy with cataplexy, now called narcolepsy type 1, are positive for the HLA-DQB1*0602 genotype. Narcolepsy is diagnosed with an overnight PSG immediately followed by a Multiple Sleep Latency Test (MSLT), looking for mean sleep latency of 8 minutes or less *and* either two or more sleep-onset REM episodes during the MSLT or sleep-onset REM on the overnight PSG (if cataplexy is present).[1] Narcolepsy type 1 can also be diagnosed on the basis of a decreased CSF hypocretin/orexin level.

Secondary narcolepsy can also occur in patients with multiple sclerosis or neuromyelitis optic spectrum disorder with hypothalamic lesions or in autoimmune encephalitis (e.g., anti-Ma2 paraneoplastic encephalitis, which can occur in patients with testicular tumors).[2–4]

Cataplexy can be seen in other conditions, such as Niemann–Pick disease type C; Angelman syndrome; Prader–Willi syndrome; myotonic dystrophy; and autosomal dominant cerebellar ataxia, deafness, and narcolepsy (ADCA-DN) due to *DNMT1* mutations (which can also cause hereditary sensory and autonomic neuropathy type 1E).[2]

### 2. C

Newborns sleep for approximately 16–20 hours per day. They spend approximately 50% of the time asleep in REM sleep, and they enter sleep through REM. Adults usually enter sleep through stage N1, and REM does not occur until approximately 60–90 minutes after sleep onset.

Sleep efficiency decreases with age. There is an increase in the number of awakenings as one becomes older.

The elderly spend more time in stage N2 sleep and less time in stage N3 sleep than younger adults do.

### 3. D

Morning vomiting is concerning for increased intracranial pressure.

Symptoms of OSA include diaphoresis, a dry mouth on awakening, arousals due to choking, and morning headaches. Retention of carbon dioxide causing cerebral vasodilation may contribute to morning headaches.

OSA is associated with cognitive impairment; cardiovascular, cerebrovascular, and endocrine diseases; pulmonary hypertension; and increased mortality.

### 4. A

Children with OSA may not appear sleepy. They may be hyperactive.

Adenotonsillar enlargement is common in children with OSA. Often, children continue to have some degree of OSA after tonsillectomy and adenoidectomy.

Allergies are a more common cause of OSA in children than in adults.

The Mallampati system is a way to describe the airway on exam and can help predict risk for sleep-disordered breathing. Craniofacial abnormalities and decreased upper airway tone also contribute to OSA. For instance, patients with Pierre Robin syndrome, which causes micrognathia, are at increased risk. Patients with Down syndrome have a number of anatomic abnormalities that contribute to OSA, such as macroglossia, upper airway hypotonia, and micrognathia. Patients with cleft palate, choanal atresia, achondroplasia, Prader–Willi syndrome, mucopolysaccharidoses, Apert syndrome, Crouzon syndrome, hypothyroidism, or Chiari malformations are also at increased risk for OSA.

In children with OSA, intermittent or prolonged partial obstruction is more common than the recurrent obstruction seen in adults.

The diagnosis of adult OSA requires an apnea–hypopnea index (AHI) of at least five events per hour, but for children the diagnosis requires an AHI of more than one event per hour. Children may also be diagnosed with OSA on the basis of periods of obstructive hypoventilation (long periods of high end-tidal or transcutaneous carbon dioxide levels during sleep) even in the absence of discrete apneas and hypopneas.

### 5. A

This patient has sleep terrors disorder, which occurs most frequently between ages 4 and 12 years and usually resolves during adolescence. It can occur in adulthood,

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most often between ages 20 and 30 years. Sleep terrors occur out of slow-wave sleep and are more common during the first half of the night. Patients with sleep terrors appear terrified; demonstrate autonomic activation such as tachycardia, tachypnea, or diaphoresis; and cannot be consoled. If they are awakened, they are confused. They do not have memory of the event.

### 6. D

Patients with excessive daytime sleepiness may fall asleep in an atypical setting or fall asleep unintentionally. There are a multitude of etiologies, such as medical (including psychiatric) disorders, disorders related to medications or other substances, and sleep-related disorders. The cause may be too little sleep, poor-quality sleep, or a primary hypersomnia.

OSA is a common cause of excessive daytime sleepiness. The STOP-BANG questionnaire screens for OSA. Snoring is just one criterion (see Box 27.1).[5] In addition to anatomic features, a number of other factors can contribute to snoring, including sleep deprivation and alcohol use.

#### *Box 27.1* THE STOP-BANG QUESTIONNAIRE (SCREEN FOR OBSTRUCTIVE SLEEP APNEA) CRITERIA

- *S*noring loudly
- *T*iredness during the day
- *O*bserved apnea
- *P*ressure (blood) is elevated.
- *B*ody mass index >35
- *A*ge >50 years
- *N*eck circumference >40 cm
- *G*ender is male.

Polysomnography is used to diagnose OSA. Some patients are eligible for home sleep testing (HST). However, HST is not recommended for patients with certain pulmonary, cardiac, and neuromuscular diseases.

Effective treatments for OSA are tonsillectomy and adenoidectomy in children and continuous positive airway pressure. Other treatments for OSA include weight loss, positional therapy, treatment of nasal congestion, oral appliances including mandibular advancement devices and tongue-retaining devices, hypoglossal stimulation, uvulopalatopharyngoplasty and other surgeries, and other devices that deliver positive airway pressure.[6,7]

### 7. False

Treatment for narcolepsy includes trying to improve sleep at night and, if possible, taking scheduled short naps in the afternoon.

Stimulants have been used to promote wakefulness in patients with narcolepsy, but modafinil and armodafinil (the R-enantiomer of modafinil) have fewer cardiac side effects. Pitolisant and solriamfetol have also been used to treat narcolepsy. Pitolisant is a histamine-3 receptor antagonist/inverse agonist. Solriamfetol is a dopamine and norepinephrine reuptake inhibitor.

Sodium oxybate (the sodium salt of γ-hydroxybutyrate [GHB]) and mixed-salt oxybate are used to treat narcolepsy and cataplexy. GHB is both a precursor and a metabolite of GABA. It binds to $GABA_B$ (and GHB) receptors.[8] SSRIs, serotonin–norepinephrine reuptake inhibitors (SNRIs), and TCAs have also been used to treat cataplexy.

### 8. B

This patient has REM sleep behavior disorder (RBD), which is characterized by recurrent episodes of dream enactment. The normal atonia characteristic of REM sleep is not present in patients with RBD.

In contrast to sleepwalking, the eyes are usually closed with RBD, and patients with RBD usually do not leave the bedroom. Because the events occur during REM sleep, they are more common in the second half of the night, when REM sleep is more prominent (unless the patient also has narcolepsy).

RBD is much more prominent in men than in women. It tends to occur in patients older than age 55 years. Patients with synucleinopathies (e.g., Parkinson disease) are at risk for RBD. Likewise, patients with RBD are at risk for synucleinopathies.

Patients with RBD should be prevented from hurting themselves or their bed partners. Melatonin and clonazepam are useful in treating RBD. Pramipexole has also been used. Transdermal rivastigmine has been used in patients with RBD and mild cognitive impairment and in patients with RBD and Parkinson disease.[9]

Medications can also trigger RBD. These include SNRIs such as venlafaxine; TCAs; SSRIs; and MAOIs. Withdrawal of REM-suppressing medications can also produce RBD. Alcohol, drugs, and caffeine can contribute to RBD.

### 9. B

This patient most likely has restless leg syndrome (RLS), which may be caused by iron deficiency. The patient's ferritin level and transferrin saturation percentage should be checked. If they are low to low-normal, an iron supplement should be prescribed.

RLS is the most common sleep-related movement disorder. RLS is characterized by a need to move the legs, especially in the evening. The patient may have an uncomfortable sensation in the legs. Symptoms are worse when the patient is at rest, and they improve with activity.

RLS is more common in women than in men. Multiple genes have been linked to RLS, most commonly *BTBD9* on chromosome 6. Conditions associated with RLS include pregnancy, peripheral neuropathy, and end-stage renal disease. Caffeine, nicotine, and alcohol

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worsen RLS. Also, dopamine antagonists, SSRIs, opioid withdrawal, benzodiazepine withdrawal, and antihistamines can worsen it.

RLS is frequently associated with increased periodic limb movements in sleep, but polysomnography is not required to diagnose RLS.

Sleep-related rhythmic movement disorder is another sleep-related movement disorder. It usually occurs in children and may manifest as head-banging or body-rocking during or while falling asleep. In severe cases, clonazepam has been used for treatment of sleep-related rhythmic movement disorder.

Some movement disorders improve in sleep; however, choreoathetosis due to Huntington disease, palatal myoclonus, and tics can continue during sleep.

**10. D**

Dopaminergic agents, calcium channel $\alpha_2\delta$ ligands, benzodiazepines, and opioids have been used to treat RLS. Dopaminergic agents and calcium channel $\alpha_2\delta$ ligands are preferred.[10] Opioids have abuse potential. SSRIs can worsen RLS, but bupropion does not. Antihistamines can worsen RLS.[11] This includes diphenhydramine, which is in many over-the-counter sleep aids.

Calcium channel $\alpha_2\delta$ ligands include gabapentin and pregabalin. They can cause sleepiness and weight gain. There is a risk of serious breathing problems in patients taking gabapentin or pregabalin who have respiratory risk factors.[12]

Dopaminergic agents such as pramipexole and ropinirole can cause nausea, sudden sleepiness, postural hypotension, leg edema, and impulse-control disorders such as compulsive gambling or shopping. Augmentation of RLS symptoms can also occur with dopaminergic agents. For instance, symptoms may begin earlier in the evening, involve additional areas of the body, or worsen. The rotigotine patch, which is a longer acting formulation, may be helpful in these cases if other treatments are not feasible.[11]

**11. E**

Some patients cannot snore. For instance, some patients with neuromuscular conditions are unable to produce enough force to produce snoring. Therefore, lack of snoring does not rule out OSA. Patients with certain neuromuscular conditions may be at risk for central apnea as well as OSA.

Insomnia is difficulty falling asleep or staying asleep to the point that there is daytime impairment. Multiple factors contribute to insomnia.

Paradoxical insomnia occurs when patients believe they have been awake but actually have been sleeping. Actigraphy and polysomnography can aid in this diagnosis.

**12. E**

Clonazepam is a treatment for severe cases of somnambulism.

Somnambulism usually begins during the first decade of life, but it can begin in adulthood. It typically occurs out of slow-wave sleep; therefore, it is more prominent in the first third of the night. Patients appear confused when getting out of bed and are confused if awakened. Their eyes are open during the event, and they may leave the bedroom.

Genetics may contribute. If one or both parents have a history of somnambulism, the child is at increased risk. Sleep deprivation is one of the most common risk factors for somnambulism. Alcohol and stress also increase one's risk. Medications that can precipitate somnambulism include hypnotics, antihistamines, anticholinergics, sodium oxybate, stimulants, and lithium. Zolpidem can cause amnesia, sleepwalking, sleep driving, and sleep eating.

Sleep hygiene and stress management are used to treat sleepwalking. For severe cases, benzodiazepines have been used.

**13. B**

Circadian rhythm sleep disorders are characterized by chronic difficulty being awake or asleep at appropriate times. Examples include advanced sleep phase disorder, delayed sleep phase disorder, jet lag disorder, non–24-hour sleep–wake disorder, irregular sleep–wake rhythm disorder, and shift work disorder. Patients with advanced sleep phase disorder fall asleep early in the evening and wake up early in the morning. Patients with delayed sleep phase disorder cannot fall asleep until late at night and then sleep late. Patients with irregular sleep–wake rhythm disorder have disorganized sleep. They have multiple sleep and wake periods within 24 hours.

Treatments for circadian rhythm sleep disorder include chronotherapy (in which the time at which one goes to sleep is gradually shifted), carefully timed phototherapy, and melatonin. In addition, night shift workers should nap before their shift and may benefit from stimulants such as caffeine or modafinil during their shift.

Tasimelteon, a melatonin receptor agonist, has been approved by the U.S. Food and Drug Administration for non–24-hour sleep–wake disorder in adults and for sleep disturbances in patients with Smith–Magenis syndrome.

**14. C**

Ramelteon is a treatment for sleep-onset insomnia. It is a selective melatonin receptor agonist. Due to drug interactions, it is recommended that ramelteon *not* be prescribed to patients who are taking fluvoxamine (which is a strong CYP1A2 inhibitor).

**15. A**

Zolpidem (Ambien) does not increase slow-wave sleep. Gabapentin, mirtazapine, pregabalin, and trazodone do increase slow-wave sleep. Priapism is a possible side effect of trazodone.

**16. A**

Doxepin is a selective histamine $H_1$ receptor antagonist. It is used for sleep maintenance. It should be avoided in patients who are taking MAOIs.

Ramelteon, which is a selective melatonin receptor agonist, is used for sleep-onset insomnia. Zaleplon and zolpidem are benzodiazepine receptor agonists that are not themselves benzodiazepines. They are also useful for sleep initiation. There is an extended-release formulation of zolpidem that is more helpful for sleep maintenance than the oral spray formulation.

**17. C**

The number of required hours of sleep varies from person to person. Therefore, the definition of hypersomnia is not based on the duration of time asleep. Hypersomnia refers to the inability to maintain alertness during waking hours. Modafinil has been used to treat idiopathic hypersomnia in adults. In vitro, modafinil acts at the dopamine transporter and prevents dopamine reuptake.

Fatigue is not synonymous with sleepiness. It is more indicative of lack of energy.

**18. D**

Usually there is less epileptiform activity during REM sleep than during other stages of sleep (see Box 27.2).

***Box 27.2*** **FEATURES OF REM SLEEP**

- Low or absent muscle tone on submental electromyography
- Rapid eye movements
- Sawtooth waves (sharply contoured waves over the central leads in the theta frequency range)
- Low-voltage, mixed-frequency EEG
- Irregular breathing
- Decrease in epileptiform activity
- Somatic muscle atonia

**19. D**

There are a number of conditions or situations in which a patient without narcolepsy can have sleep-onset REM. Examples include sleep deprivation or deprivation of REM sleep, circadian rhythm disorder, and withdrawal of medications that suppress REM.

SSRIs such as fluoxetine, TCAs such as protriptyline and imipramine, and the SNRI venlafaxine suppress REM. They have been used in the treatment of cataplexy.

**20. C**

Sleep drunkenness is prolonged grogginess and difficulty becoming alert after awakening from sleep.

Sleep deprivation can cause functional impairment in certain tasks similar to alcohol intoxication.

Exploding head syndrome is a parasomnia that is more frightening than painful.

Hypnic headache is a primary headache disorder that occurs in older adults. Patients describe a throbbing headache starting during sleep, which may be unilateral or bilateral. Hypnic headaches can occur in REM and non-REM sleep.

**21. B**

Cognitive–behavioral therapy is helpful in treating insomnia. It includes a number of different behavioral therapy components, such as sleep restriction therapy, relaxation therapy, and stimulus control therapy. During sleep restriction therapy, the patient limits the amount of time spent in bed in order to reduce the time to sleep onset. During stimulus control therapy, the bed is used almost exclusively for sleep, and the patient lies down only when sleepy.

**22. D**

Patients with cluster headache do have an increased risk of OSA. The risk is even greater if the patient is overweight. Treatment of OSA in these patients may result in improvement in their cluster headaches.

Patients who have had a transient ischemic attack or stroke should be assessed for sleep-disordered breathing, which is a risk factor for stroke.

**23. B**

To be diagnosed with enuresis, the child should be at least 5 years of age.

There is a link between OSA and enuresis. Enuresis may have a genetic component. Desmopressin has been used to treat enuresis.

**24. D**

Non-REM parasomnias usually occur in the first half of the night, when non-REM sleep predominates. They tend to occur from stage N3 sleep.

Most nocturnal frontal lobe seizures occur outside of non-REM sleep, usually in stage N2, but they also can occur from stage N1. They can occur at any time of the night. They are brief and stereotyped, may occur multiple times per night, and are not typically associated with postevent confusion. These features aid in distinguishing them from non-REM parasomnias. Sometimes no EEG correlate is seen with nocturnal frontal lobe seizures, so EEG does not always differentiate the entities.

**25. D**

Recurrent isolated sleep paralysis is a REM sleep disorder (see Boxes 27.3 and 27.4).

***Box 27.3*** **NON-REM SLEEP DISORDERS**

- Confusional arousals
- Sleep terrors
- Sleepwalking

### *Box 27.4* REM SLEEP DISORDERS

- REM sleep behavior disorder
- Recurrent isolated sleep paralysis
- Nightmare disorder

Image rehearsal therapy, a type of cognitive–behavioral therapy, has been used to treat nightmare disorder. Prazosin, which is an $\alpha_1$-adrenergic receptor antagonist, has been used to treat nightmares in patients with post-traumatic stress disorder. Prazosin can cause orthostatic hypotension.

**26. A**

Sympathetic activation is helpful in differentiating sleep terrors from other parasomnias.

**27. C**

The suprachiasmatic nucleus of the hypothalamus, which is in the ventral–anterior region of the hypothalamus, controls circadian rhythms. Melatonin receptors are prevalent in the suprachiasmatic nucleus, which receives input from the retinohypothalamic tract. Lesions in the suprachiasmatic nucleus cause abnormal sleep–wake, eating, and temperature rhythms.

**28. A**

Patients with Alzheimer's disease may have sleep–wake disturbances due to damage to cholinergic neurons in the suprachiasmatic nucleus and ventrolateral preoptic nucleus.

Damage to the sublaterodorsal tegmental nucleus is associated with RBD.[13]

**29. B**

During sleep, neurons in the arousal system are inhibited by GABA and galanin.

There are two branches/pathways of the ascending arousal system. Both start in the upper pons and activate the cerebral cortex. There are monoaminergic and cholinergic neurons in the ascending arousal system.

The dorsal pathway is from the pons to the thalamus. Specifically, cholinergic neurons in the pedunculopontine tegmental nucleus (PPT) and the laterodorsal tegmental nucleus (LDT) innervate the thalamus, including the reticular nucleus. The final result is thalamocortical transmission and cortical activation.

The ventral pathway is from the pons through the hypothalamus to the basal forebrain and cortex. It consists primarily of monoaminergic neurons—neurons in the locus coeruleus (norepinephrine), dorsal and median raphe nuclei (serotonin), parabrachial nucleus and precoeruleus area (glutamate), periaqueductal gray matter (dopamine), and tuberomammillary nucleus (histamine).

Neurons in the lateral hypothalamus that produce orexin/hypocretin are also involved in wakefulness. They innervate the components of the ascending arousal system and the cerebral cortex. Loss of orexin neurons causes narcolepsy.[13] Dual orexin receptor antagonists such as daridorexant, lemborexant, and suvorexant have been used to treat insomnia. (See Box 27.5 and Table 27.1.)

### *Box 27.5* NEUROTRANSMITTERS AND NEUROPEPTIDES INVOLVED IN WAKEFULNESS

- Acetylcholine
- Dopamine
- Glutamate
- Histamine
- Hypocretin/orexin
- Norepinephrine
- Serotonin

### *Table 27.1* LOCATION OF SPECIFIC NEUROTRANSMITTERS/NEUROPEPTIDES

| NEUROTRANSMITTER/ NEUROPEPTIDE | LOCATION OF NEURONS |
|---|---|
| **Acetylcholine** | **Pedunculopontine tegmental nucleus (PPT) and laterodorsal tegmental nucleus (LDT)** |
| **Dopamine** | **Substantia nigra** |
| **Glutamate** | **Parabrachial nucleus and precoeruleus area** |
| **Histamine** | **Tuberomammillary nucleus** |
| **Hypocretin/orexin** | **Lateral hypothalamus** |
| **Norepinephrine** | **Locus coeruleus** |
| **Serotonin** | **Dorsal and median raphe** |

**30. C**

The ventrolateral preoptic nuclei (VLPO) and median preoptic nuclei (MNPO) inhibit the arousal system during sleep. Neurons of the VLPO release galanin and GABA; those of the MNPO release GABA (see Box 27.6).

### *Box 27.6* NEUROTRANSMITTERS INVOLVED IN SLEEP

- Acetylcholine (REM sleep)
- Adenosine
- GABA
- Galanin

Neurotransmitters involved in sleep include acetylcholine (REM sleep), adenosine, GABA, and galanin. Caffeine promotes wakefulness by blocking the adenosine receptor.[13]

**31. C**

Neurons in the pons cause REM sleep. Specifically, neurons in the subcoeruleus area/sublaterodorsal nucleus and precoeruleus region of the pons generate REM sleep. These neurons are glutamatergic. Neurons in this region promote atonia, rapid eye movements, and EEG desynchronization during REM sleep. For instance, atonia is caused by descending projections from this region to the ventromedial medulla and spinal interneurons that hyperpolarize alpha motor neurons. Cholinergic neurons in the laterodorsal tegmental nuclei (LDT) and the pedunculopontine tegmental nuclei (PPT) are also REM-on cells; they promote REM, including REM atonia.[14,15]

Neurons in the pons that cause REM sleep are inhibited by neurons in the lower midbrain, which act as REM-off neurons.

The dorsal raphe, locus coeruleus, and tuberomammillary nucleus are involved in the arousal system, which is inhibited during sleep.[13]

**32. A**

The vlPAG/LPT areas stop REM. They inhibit the sublaterodorsal nucleus and precoeruleus neurons and are inhibited by them.

The LDT and PPT promote REM.[13] (See Box 27.7.)

The VLPO and MNPO promote sleep.

***Box 27.7*** **STRUCTURES THAT PROMOTE REM SLEEP**

- Parabrachial nucleus/precoeruleus area (glutamatergic, in the pons)
- Laterodorsal tegmental nuclei (LDT) and pedunculopontine tegmental nuclei (PPT) (cholinergic, in the pons at the junction with the midbrain)
- Subcoeruleus area/sublaterodorsal nucleus (glutamatergic, in the pons)

**33. A**

Sleep diaries are a means of documenting sleep and wake times. They are helpful in the diagnosis of circadian rhythm disorders.

**34. A**

An actigraph measures movement and acts as an indirect measure of alertness. Actigraphy is helpful in diagnosis of circadian rhythm disorder; insomnia, including paradoxical insomnia; and periodic limb movements. It also can be used to assess the effectiveness of treatment of these conditions.

Actigraphy is also helpful if insufficient sleep syndrome is suspected. Insufficient sleep syndrome is classified as a type of central disorder of hypersomnolence. In this condition, sleep is chronically voluntarily curtailed; patients regularly sleep less time than is recommended as a result of their behaviors. Their sleepiness improves when sleep time is extended.

**35. A**

The Multiple Sleep Latency Test (MSLT) and the maintenance of wakefulness test (MWT) are not validated in children younger than age 5 years.

MSLT is helpful in the assessment of daytime sleepiness and in the diagnosis of narcolepsy. A PSG is performed the night before an MSLT. During the MSLT, the patient is instructed to try to fall asleep during five naps at 2-hour intervals. A mean sleep latency of less than 8 minutes is indicative of excessive daytime sleepiness. This finding plus either two sleep-onset REM periods during the MSLT or sleep-onset REM on the preceding PSG can be used to diagnose narcolepsy in the appropriate clinical setting.[1]

An MWT is an objective, structured test that is used to determine whether a patient can remain awake. The patient tries to stay awake during four 40-minute trials. A mean sleep latency of less than 8 minutes suggests excessive daytime sleepiness. A PSG is not required the night before an MWT.

**36. B**

This patient has Kleine–Levin syndrome, which is characterized by episodes of hypersomnia lasting for 2 days to 4 weeks that recur at least once per year. Patients may sleep for 15–21 hours per day. They are normal between episodes. During the episodes, patients are confused and have unusual behavior. Apathy is common. Hyperphagia, hypersexuality, hallucinations, or derealization may occur. The first episode may be triggered by an infection. EEG obtained during an episode typically shows background slowing. Single-photon emission computed tomography shows dysfunction of the frontal and temporal lobes, thalamus, and hypothalamus during the episodes.[16] Lithium has been used to treat Kleine–Levin syndrome. If prescribed, lithium levels should be monitored. Potential side effects of lithium include tremor, polyuria, polydipsia, diarrhea, and subclinical hypothyroidism.[17]

Multiple sleep disorders have been associated with immunoglobulin-like cell adhesion molecule 5 (IgLON5) autoantibodies, including OSA, REM behavior disorder, non-REM parasomnias, and stridor.[4,18] “Finalistic behavior” (work-related behavior) in sleep has been described. Patients also can have chorea, cognitive changes, vertical supranuclear gaze palsy, and bulbar symptoms.[18]

*PHOX2B* mutations are the most common cause of congenital central hypoventilation syndrome (CCHS), which is characterized by central hypoventilation and autonomic nervous system dysregulation. CCHS has been referred to as Ondine’s curse, although this term has been used for other conditions in the past as well.

There are overlapping symptoms between Kleine–Levin syndrome and rapid-onset obesity with hypoventilation, hypothalamic dysfunction, autonomic dysregulation (ROHHAD) syndrome; however, Kleine–Levin syndrome is episodic, and ROHHAD syndrome usually presents in early childhood with rapid obesity and is associated with hypoventilation.

There are overlapping features between ROHHAD syndrome and congenital central hypoventilation syndrome, such as autonomic dysfunction and potentially life-threatening hypoventilation. In addition, patients with either condition can develop neural crest tumors. Hypothalamic dysfunction helps differentiate patients with ROHHAD syndrome from patients with CCHS. Also, CCHS is often associated with *PHOX2B* mutations.

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# 28.

# SUBSTANCE-RELATED DISORDERS

## QUESTIONS

1. **Which substance is *not* covered by a substance use diagnosis in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5 and DSM-5-TR)?**
   A. Alcohol
   B. Caffeine
   C. Cannabis
   D. Tobacco

2. **True or false?**
   According to the DSM-5 and DSM-5-TR, a patient who experiences tolerance and withdrawal to a substance is addicted to that substance.

3. **Which of the following medications inhibits aldehyde dehydrogenase and has been used to treat alcohol dependence but requires abstention from alcohol in medicines and desserts in order to avoid unpleasant symptoms?**
   A. Naloxone
   B. Naltrexone
   C. Flumazenil
   D. Methadone
   E. Disulfiram

4. **A 56-year-old woman presents with symptoms of confusion, wide-based gait, and dysconjugate gaze. She has a noticeable smell of alcohol. What is the most appropriate initial treatment?**
   A. Lorazepam
   B. Diazepam
   C. Thiamine
   D. Buprenorphine

5. **A 40-year-old man presents to the emergency department with confusion. His family reports recent problems with diarrhea and a history of alcoholism. On examination, he is thin and appears to have a sunburn on his face, chest, and hands, but the family denies significant sun exposure. Which of the following diagnoses should be considered?**
   A. Beriberi
   B. Lupus
   C. Pellagra
   D. Dermatomyositis

6. **A 50-year-old man is admitted for confusion. The family reports a long history of alcoholism. Every day he reintroduces himself. When asked the date, he says, “Time flies doesn’t it?” He seems to invent answers to questions. Which of the following diagnoses is most likely?**
   A. Early onset Alzheimer disease
   B. Korsakoff syndrome
   C. Wet beriberi
   D. Alcohol-induced fugue state

7. **As a result of decreasing ethanol levels, patients can have which of the following signs of withdrawal even while still intoxicated?**
   A. Autonomic hyperactivity
   B. Seizure
   C. Tremor
   D. Delirium tremens

8. **Which of the following can occur with chronic alcohol use?**
   A. Demyelination of the corpus callosum
   B. Myopathy
   C. Neuropathy
   D. All of the above

9. **Which of the following features is characteristic of fetal alcohol syndrome?**
   A. Short palpebral fissures, thin upper lip, and smooth philtrum
   B. Growth deficiency
   C. Hyperactivity, inattention, and cognitive impairment
   D. All of the above

10. **Which of the following medications is most dangerous to use in a patient with acute cocaine intoxication?**
    A. Benzodiazepines
    B. β-Blockers
    C. Calcium channel blockers
    D. Diuretics

11. **Which of the following statements correctly describes a difference between 3,4-methylenedioxymethamphetamine (MDMA) and cocaine?**
    A. MDMA does not cause hallucinations.
    B. MDMA has more dopaminergic activity than cocaine.
    C. MDMA has more serotonergic activity than cocaine.
    D. MDMA does not have long-term side effects.

12. **At which receptor does lysergic acid diethylamide (LSD) primarily act?**
    A. Norepinephrine
    B. Epinephrine
    C. Dopamine
    D. Serotonin
    E. Glutamate

13. **Which of the following is *least* likely to cause stroke?**
    A. γ-Hydroxybutyrate (GHB)
    B. Heroin
    C. Lysergic acid diethylamide (LSD)
    D. Phencyclidine (PCP)
    E. Cannabis/marijuana

14. **Which inhalant is most likely to cause myeloneuropathy?**
    A. Gasoline
    B. Hexane
    C. Nitrous oxide
    D. Toluene
    E. Trichloroethylene

15. **A 20-year-old postoperative patient is difficult to arouse. On examination, his pupils are pinpoint, and he has slowed respirations. Which of the following medications is most likely to be diagnostic and therapeutic?**
    A. Diphenhydramine
    B. Dopamine
    C. Epinephrine
    D. Naloxone

16. **Which of the following is *least* likely to occur during opioid intoxication?**
    A. Hypersexuality
    B. Hypothermia
    C. Postural hypotension
    D. Vomiting

17. **Which of the following statements about heroin use is true?**
    A. Heroin is metabolized to morphine.
    B. Heroin can cause a myelopathy resembling anterior spinal artery syndrome.
    C. Heroin can be associated with vertebral osteomyelitis.
    D. Heating heroin and inhaling the vapor can cause spongiform encephalopathy.
    E. All of the above.

18. **Which of the following is *least* likely to cause agitated delirium in adults?**
    A. Anticholinergic medications
    B. Opioid withdrawal
    C. Nicotine
    D. Phencyclidine (PCP)
    E. Synthetic cathinones

19. **Which of the following medications is most useful in blocking the side effects of opioid withdrawal?**
    A. Clonidine
    B. Diphenhydramine
    C. Propranolol
    D. Verapamil

20. **Which of the following is most likely to cause seizures, delirium, myoclonus, and tremor?**
    A. Fentanyl
    B. Meperidine
    C. Morphine
    D. Oxycodone

21. **What is the mechanism of action for PCP?**
    A. It is an α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) agonist.
    B. It is an *N*-methyl-D-aspartate (NMDA) antagonist.
    C. It is a serotonin receptor agonist.
    D. It is a dopamine receptor agonist.

22. **Which of the following statements is *false* regarding PCP?**
    A. PCP can cause a schizophrenia-like syndrome.
    B. PCP intoxication can cause rhabdomyolysis.
    C. PCP intoxication can cause severe agitation.
    D. PCP raises the seizure threshold.

23. **A child presents with altered mental status, diaphoresis, salivation, vomiting, and diarrhea. Which of the following is the most likely cause?**
    A. Belladonna
    B. *Datura stramonium*
    C. Nitrous oxide
    D. Tobacco

24. **Which of the following is *least* likely to occur in patients who use MDMA?**
    A. Acute toxic leukoencephalopathy
    B. Cerebral edema
    C. Dystonic reaction
    D. Hyponatremia
    E. Hypothermia

25. **Which of the following is *false* regarding cannabinoids?**
    A. Chronic cannabinoid use has been associated with a hyperemesis syndrome.
    B. Synthetic cannabinoids can cause seizures.
    C. Synthetic cannabinoids can cause psychosis.
    D. Synthetic cannabinoids cause lethargy and apathy.
    E. Tetrahydrocannabinol produces the psychoactive effects associated with cannabis/marijuana.

# SUBSTANCE-RELATED DISORDERS

## ANSWERS

### 1. B

In the DSM-5 and DSM-5-TR, substance abuse and substance dependence are not differentiated. They use the term *substance use disorder*. Gambling disorder is also included among the substance-related and addictive disorders.

For diagnosis of a substance use disorder, there must be evidence of pathologic behaviors regarding the substance, such as impaired control, effects on relationships or obligations, or continued use despite risk. Tolerance and withdrawal are also among the criteria, but they are not required for the diagnosis.

Caffeine intoxication and caffeine withdrawal are diagnoses in the DSM-5 and DSM-5-TR, but caffeine use disorder is not an established diagnosis. It is mentioned as a condition for further study.

In addition to defining substance use disorders, the DSM-5 and DSM-5-TR discuss substance-induced disorders such as intoxication, withdrawal, sexual dysfunction, mood disorders (psychotic, bipolar, depressive, and obsessive–compulsive), sleep disorders, delirium, and neurocognitive disorders.[1,2]

### 2. False

The term "addiction" is not used in the DSM-5 or DSM-5-TR.[1,2] The need for increasing doses to achieve the same effect indicates tolerance. Most substances have a typical withdrawal syndrome. Withdrawal involves experiencing physical, cognitive, and behavioral symptoms due to reducing or halting substance use, and these symptoms must not be due to another mental or medical conditions.

### 3. E

Ethanol is metabolized by alcohol dehydrogenase to acetaldehyde, which is metabolized by aldehyde dehydrogenase to acetic acid.

Disulfiram (Antabuse) inhibits aldehyde dehydrogenase, resulting in the accumulation of acetaldehyde if alcohol is ingested. This causes flushing, nausea, and vomiting. Disulfiram can be associated with a peripheral neuropathy.

Flumazenil is a benzodiazepine antagonist.

Naloxone and naltrexone are opioid antagonists. Methadone is a long-acting opioid agonist and is approved by the U.S. Food and Drug Administration for opioid use disorder.

### 4. C

This patient has symptoms concerning for Wernicke encephalopathy (cognitive changes, ataxia, and disturbances in extraocular movements), which occurs in patients with thiamine deficiency. Patients who abuse alcohol are at risk for thiamine deficiency. To avoid Wernicke encephalopathy in patients who might be at risk for the condition, thiamine should be administered before intravenous fluids with glucose. Wernicke encephalopathy represents the acute phase of the disorder, and Korsakoff syndrome is characterized by chronic amnesia.

Wernicke encephalopathy causes magnetic resonance imaging changes such as fluid-attenuated inversion recovery (FLAIR) abnormalities in the thalamus, mammillary bodies, periaqueductal gray region, and tectum.

Buprenorphine is a partial agonist at mu-opioid receptors. It is used in opioid use disorder.

Diazepam and lorazepam are both benzodiazepines, with diazepam being longer acting.

### 5. C

Patients who abuse alcohol are at risk for niacin deficiency, which manifests as pellagra. Patients with pellagra have characteristic skin findings, dementia, and diarrhea.

Niacin deficiency should be considered in alcoholic patients with continued encephalopathy despite thiamine.[3]

Vitamin $B_{12}$ and vitamin $B_6$ may also be deficient in patients who chronically abuse alcohol.

Beriberi is discussed below.

### 6. B

Korsakoff syndrome is an amnestic syndrome that is caused by thiamine deficiency and is characterized by both retrograde and anterograde amnesia. Confabulation is characteristic.

Beriberi is caused by thiamine deficiency. Dry beriberi affects the nervous system and can present with symptoms such as difficulty walking, numbness, weakness, confusion, pain, speech difficulties, abnormal eye movements, tingling, and vomiting. Wet beriberi affects the cardiovascular system and can present with symptoms such as palpitations, shortness of breath, and leg swelling.

Alcohol intoxication can cause symptoms similar to the psychiatric condition dissociative amnesia (inability to recall key autobiographical information). This psychiatric condition can be associated with dissociative fugue (travel or wandering associated with amnesia).[2] A dissociative fugue would not explain this patient's persistent anterograde amnesia.

**7. B**

Seizures and tremor are early signs of alcohol withdrawal. Patients can have a seizure due to decreasing ethanol levels while still intoxicated.

Delirium tremens is a later sign of withdrawal. Patients can develop delirium tremens without having earlier signs. Delirium tremens is characterized by agitation, altered mental status, hallucinations, and autonomic hyperactivity. Benzodiazepines are the treatment of choice.

Benzodiazepine and barbiturate withdrawal cause symptoms similar to ethanol withdrawal. All three act at the $\gamma$-aminobutyric acid A ($GABA_A$) receptor. Symptoms of withdrawal include hallucinations, agitation, seizures, and diaphoresis.

**8. D**

Chronic alcohol use can cause multiple neurologic problems. It can cause dementia characterized by global impairment. Alcohol can cause both an acute and a chronic myopathy. It can cause neuropathy either due to direct toxic effects or due to nutritional deficiencies. Alcohol intoxication is a risk factor for compressive neuropathies such as Saturday night palsy due to compression of the radial nerve. In addition, chronic alcohol use causes cerebellar degeneration; typically, the superior vermis is most affected. Liver damage due to chronic alcohol use also has neurologic complications. Less commonly, chronic alcohol use can cause Marchiafava–Bignami disease, which is characterized by corpus callosum demyelination.

Marchiafava–Bignami disease can cause ataxia and hyperreflexia. Dementia can occur. Some patients present with coma.

In addition to affecting the cardiovascular and gastrointestinal systems, alcohol suppresses the immune system. Alcohol is a risk factor for infection with *Streptococcus pneumoniae*, which can cause endocarditis, pneumonia, and meningitis. Alcohol is also a risk factor for *Listeria monocytogenes* meningitis.

**9. D**

Fetal alcohol syndrome causes craniofacial abnormalities, growth deficiency, and cognitive impairment. Children with fetal alcohol syndrome often have microcephaly as well as short palpebral fissures, a smooth philtrum, and a thin upper lip. They have impaired growth and developmental delay. They often demonstrate hyperactivity, inattention, impaired executive function, and intellectual disability.

**10. B**

β-Blockers should be avoided in patients with acute cocaine intoxication because they can cause paradoxical hypertension due to unopposed alpha stimulation.

**11. C**

MDMA, also known as Ecstasy, has properties similar to those of an amphetamine and a hallucinogen, specifically mescaline. Compared with cocaine or methamphetamine, MDMA has more serotonergic activity. Cocaine and methamphetamine have more dopaminergic activity than MDMA. Cognitive impairment occurs with long-term use of either cocaine or MDMA.

The main mechanism of cocaine is blocking the reuptake of dopamine, norepinephrine, and serotonin into the presynaptic neuron. Amphetamines can act similarly, but the main mechanism of amphetamines is the release of neurotransmitters from the presynaptic neuron.

**12. D**

LSD primarily acts at the serotonin receptor.

**13. A**

Of the substances listed, GHB is least likely to cause stroke.

Cocaine can cause hypertension; hemorrhagic, ischemic, or cardioembolic stroke; and vasculitis.

LSD is an ergot and can cause vasoconstriction and ischemic stroke.

PCP also causes vasoconstriction.

Heroin use can cause vasculitis and infective endocarditis leading to strokes.

Marijuana has been associated with reversible cerebral vasoconstriction and stroke.[4]

**14. C**

Nitrous oxide causes myeloneuropathy. It causes a clinical picture similar to that of vitamin $B_{12}$ deficiency, possibly because it interferes with methionine synthetase.

Inhalants that are abused tend to be volatile hydrocarbons that cause euphoria. The majority are usually not associated with a withdrawal syndrome. However, they can have significant neurological complications (see Table 28.1).

*Table 28.1* NEUROLOGIC COMPLICATIONS OF COMMON INHALANTS

| INHALANT | NEUROLOGIC COMPLICATIONS |
|---|---|
| Gasoline | Lead encephalopathy |
| Hexane | Peripheral neuropathy |
| Nitrite | Methemoglobinemia |
| Nitrous oxide | Myeloneuropathy |
| Toluene | Dementia, leukoencephalopathy, ataxia |
| Trichloroethylene | Trigeminal neuropathy |

**15. D**

This patient overdosed on an opioid. Examples of opioids include buprenorphine, codeine, fentanyl, heroin, hydrocodone, hydromorphone, meperidine, methadone, oxycodone, and tramadol. Opioid overdose produces coma with miosis and respiratory depression. Flash pulmonary edema may occur. Opioid overdose has been reported to cause acute cerebellar edema resulting in herniation.[5]

Opioid intoxication is treated with naloxone. Naloxone can precipitate opioid withdrawal in patients who are dependent on opioids.

Naloxone and naltrexone are opioid antagonists. Naltrexone has a longer half-life.

Gabapentin and pregabalin potentiate the effects of opioids.[5]

**16. A**

Opioid intoxication tends to cause decreased libido, not hypersexuality. It also is accompanied by euphoria, hypothermia, vomiting, constipation, and postural hypotension. Pruritus may occur as a result of histamine release.

**17. E**

Heroin, which is metabolized to morphine, is immunosuppressive. Injection of heroin increases the patient's risk for a number of infections, such as abscess, endocarditis, joint infections, and osteomyelitis, in addition to parenterally acquired infections. Heroin can also cause a myelopathy that resembles anterior spinal artery syndrome. Some cases of myelopathy due to heroin are associated with cerebrospinal fluid pleocytosis. Heroin can also be associated with rhabdomyolysis.[5] Heating heroin and inhaling the vapor, which has been referred to as "chasing the dragon," can cause spongiform encephalopathy. This can be associated with abulia, ataxia, quadriparesis, and blindness.[6]

**18. B**

Opioid withdrawal causes yawning, rhinorrhea, tearing, and diaphoresis followed by abdominal cramping, vomiting, diarrhea, piloerection, and mydriasis. Seizures and delirium are atypical in opioid withdrawal in adults and should raise suspicion that another substance was ingested.

Kratom, which has opioid-like properties, is a hallucinogen that is associated with withdrawal symptoms.

Anticholinergic medications can cause or exacerbate delirium, which may present as confusion, hallucinations, agitation, disorientation, or memory loss. Anticholinergic medications may also be associated with mydriasis, dry skin, and decreased bowel sounds.

Cathinone is found in khat, which is a plant. Cathinone and synthetic cathinones, including bath salts, are psychostimulants. Methcathinone contaminated with potassium permanganate has been associated with parkinsonism.[5]

**19. A**

Methadone, which is a long-acting synthetic opioid, helps prevent opioid withdrawal symptoms. Clonidine treats the autonomic symptoms.

**20. B**

Normeperidine, which is the metabolite of meperidine, can cause altered mental status, seizures, myoclonus, and tremor. High doses of other opioids can also cause myoclonus.

A meperidine derivative, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), has been associated with parkinsonism. Methcathinone, which is a psychostimulant, has also been associated with parkinsonism. Potassium permanganate, which is used to synthesize methcathinone, can cause manganese toxicity, resulting in an extrapyramidal syndrome.[5]

**21. B**

PCP is an NMDA antagonist, and it inhibits reuptake of monoamines (see Table 28.2).

*Table 28.2* SUBSTANCES AND THEIR SITES OF ACTION

| SUBSTANCE | SITES OF ACTION |
|---|---|
| Alcohol | $\text{GABA}_A$ receptor allosteric modulator |
| Amphetamines | Multiple, mainly increases neurotransmitter release (dopamine, norepinephrine, and serotonin) |
| Barbiturates | $\text{GABA}_A$ receptor allosteric modulator |
| Benzodiazepines | $\text{GABA}_A$ receptor allosteric modulator |
| Caffeine | Adenosine receptor antagonist |
| Cocaine | Multiple, mainly blocks neurotransmitter reuptake (dopamine, norepinephrine, and serotonin) |
| Dextromethorphan | NMDA receptor antagonist |
| Ketamine | NMDA receptor antagonist |
| Lysergic acid diethylamide (LSD) | Certain serotonin receptors |
| Marijuana/ tetrahydrocannabinol (THC) | Cannabinoid (CB1) receptor |
| Opioids | Mu-opioid receptors |
| Phencyclidine (PCP) | NMDA receptor antagonist, inhibits reuptake of monoamines |
| Tobacco (nicotine) | Nicotinic acetylcholine receptor agonist |

Ketamine and dextromethorphan are also NMDA receptor antagonists. Ketamine has similar but milder effects than PCP. Ketamine is a dissociative anesthetic. It can cause hypertension, increased intracranial pressure, hypersalivation, and emergence delirium.

Dextromethorphan can cause a urine drug screen to be falsely positive for PCP.

The combination of dextromethorphan and quinidine has been used to treat pseudobulbar palsy. However, this medication can cause QT prolongation. Also, monoamine oxidase inhibitors are contraindicated in patients taking this medication. Furthermore, quinidine should be avoided in patients with myasthenia gravis.

**22. D**

PCP lowers the seizure threshold; it can cause seizures. In addition, it can cause myoclonus, hypertensive encephalopathy, and ischemic and hemorrhagic stroke.

PCP was originally used as a dissociative anesthetic; however, it was discontinued as an anesthetic because it produced symptoms of psychosis. PCP can cause symptoms of schizophrenia, both positive and negative. It can cause paranoia, hallucinations, flat affect, and catatonic posturing. An emergence reaction can occur while drug elimination is in progress, resulting in return of psychosis symptoms.

PCP can cause nystagmus, hyperthermia, tachycardia, hypertension, rhabdomyolysis, and respiratory depression at higher doses.

Benzodiazepines are used for sedation in patients who have taken PCP. Before using an antipsychotic agent in a patient who has taken PCP, it should be remembered that neuroleptics can lower the seizure threshold, can worsen myoglobinuria, and can have anticholinergic side effects such as tachycardia.

**23. D**

Tobacco ingestion can cause cholinergic symptoms such as altered mental status, salivation, vomiting, and diarrhea. Atropine can treat the parasympathetic symptoms.

Belladonna and *D. stramonium* (jimson weed) can cause symptoms of anticholinergic poisoning. Anticholinergic poisoning may be treated with physostigmine. Neuroleptics have anticholinergic properties and should be avoided in anticholinergic poisoning.

Nitrous oxide is a dissociative anesthetic.

**24. E**

MDMA tends to cause hyperthermia, not hypothermia. It can also cause acute toxic leukoencephalopathy, hyponatremia, cerebral edema, and dystonic reactions.

**25. D**

Chronic cannabinoid use has been associated with a hyperemesis syndrome. Symptoms may improve with hot baths/showers.

Synthetic cannabinoids tend to have a greater stimulant effect than marijuana. They can cause diaphoresis, tachycardia, agitation, and psychosis. They also can be associated with hypokalemia and seizures. Synthetic cannabinoids can be contaminated with brodifacoum, which can cause coagulopathy and intracranial hemorrhage.[5]

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# 29.

# VITAMIN DEFICIENCY AND EXCESS

## QUESTIONS

1. **A homeless man is brought to the emergency department by the police. They say that he is confused and unsteady. On examination, he has horizontal gaze evoked nystagmus and bilateral lateral rectus muscle weakness. Which of the following vitamins is deficient in this condition?**
   A. Folate (vitamin $B_9$)
   B. Pyridoxine (vitamin $B_6$)
   C. Thiamine (vitamin $B_1$)
   D. Cobalamin (vitamin $B_{12}$)

2. **What vitamin deficiency might be indicated by the occurrence of dementia alongside symptoms such as diarrhea and a scaly rash?**
   A. Niacin
   B. Thiamine
   C. Vitamin $B_{12}$
   D. Vitamin E

3. **A 23-year-old woman presents with falls when walking in the dark. She also reports a tingling sensation from her neck down her back with neck flexion. On examination, she has decreased reflexes and decreased sensation to all modalities in the upper and lower extremities. She denies medications except for a vitamin "to give her energy and help her lose weight." Which of the following best explains her symptoms?**
   A. Pyridoxine toxicity
   B. Hypervitaminosis A
   C. Hypervitaminosis D
   D. Hypervitaminosis E

4. **Fill in the blank: Isoniazid (INH) causes ____________________ deficiency.**
   A. Vitamin $B_{12}$
   B. Pyridoxine
   C. Riboflavin
   D. Thiamine

5. **Night blindness may occur with which of the following?**
   A. Pantothenic acid (vitamin $B_5$) deficiency
   B. Riboflavin deficiency
   C. Vitamin A deficiency
   D. Vitamin C deficiency

6. **A patient with inflammatory bowel disease presents with leg paresthesias and falls. On examination, the patient has impaired vibration and position sense in the lower extremities, a positive Babinski sign bilaterally, ankle areflexia, and a positive Romberg sign. Which of the following is the most likely cause?**
   A. Selenium deficiency
   B. Vitamin $B_{12}$ deficiency
   C. Vitamin E deficiency
   D. Strachan syndrome

7. **Fill in the blank: Excess intake of ____________________ causes myeloneuropathy due to copper deficiency.**
   A. Cadmium
   B. Cobalt
   C. Lead
   D. Zinc

8. **After undergoing bariatric surgery, a 40-year-old woman develops myelopathy. A vitamin deficiency is suspected. Which of the following vitamins is *least* likely to be the culprit?**
   A. Copper
   B. Vitamin $B_{12}$
   C. Vitamin E
   D. Vitamin K

CEPIEC

# VITAMIN DEFICIENCY AND EXCESS

## ANSWERS

**1. C**

Wernicke encephalopathy is associated with a triad of ophthalmoparesis (with nystagmus), ataxia, and confusion. It is caused by thiamine (vitamin B1) deficiency and is classically seen in alcoholics. Thiamine is given in the emergency department to prevent Wernicke disease. It also can occur in other patients with malnutrition, such as patients with AIDS, cancer, or hyperemesis gravidarum; patients on long-term parenteral nutrition; and patients who have undergone bariatric surgery.

Pathologic findings in Wernicke encephalopathy are symmetric lesions of the mammillary bodies, periventricular regions of the thalamus and hypothalamus, periaqueductal gray, and superior cerebellar vermis.

If a patient with Wernicke disease is not responding to thiamine, consider hypomagnesemia. Magnesium is needed for activation of thiamine.

If there is a chronic problem with memory, the patient has Wernicke–Korsakoff syndrome. Classically, Korsakoff psychosis has been associated with confabulation.

**2. A**

Niacin deficiency causes pellagra, which is characterized by dementia, diarrhea, and a characteristic rash (dermatitis).

**3. A**

Pyridoxine causes an axonal sensory neuropathy and Lhermitte's phenomenon in high doses.

Hypervitaminosis A can cause pseudotumor cerebri/intracranial hypertension. The structure of isotretinoin (Accutane) resembles that of vitamin A, so it can cause similar symptoms. Isotretinoin is also a teratogen.

Hypervitaminosis D causes hypercalcemia and hypercalciuria.

Hypervitaminosis E can cause increased bleeding (because of its effect on vitamin K).

**4. B**

INH increases pyridoxine excretion and can cause pyridoxine deficiency, which is associated with a sensory polyneuropathy (see Box 29.1). Severe pyridoxine deficiency can cause seizures. There is a neonatal form of pyridoxine deficiency characterized by refractory seizures.

### *Box 29.1* B VITAMINS THAT CAUSE POLYNEUROPATHY

- Thiamine (deficiency)
- Pyridoxine (deficiency and toxicity)
- Pantothenic acid (deficiency)
- Vitamin $B_{12}$ (deficiency)
- Folic acid (deficiency)

**5. C**

Vitamin A deficiency can result in night blindness.

Vitamin E deficiency can cause retinitis pigmentosa, which manifests with night blindness. Other neurologic causes of retinitis pigmentosa include Refsum disease, abetalipoproteinemia, and mitochondrial diseases such as Kearns–Sayre syndrome and NARP syndrome (neuropathy, ataxia, and retinitis pigmentosa).

Pantothenic acid (vitamin $B_5$) is a precursor of coenzyme A. Deficiency causes a polyneuropathy.

Vitamin C is involved in synthesis of components of connective tissues, such as collagen. It also modulates iron absorption, transport, and storage.[1] Vitamin C deficiency causes scurvy. Patients with vitamin C deficiency develop fatigue and may refuse to walk. Other manifestations include petechiae, ecchymoses, bleeding gums, and joint and muscle pain.

**6. B**

This patient has vitamin $B_{12}$ deficiency, which predominantly affects the posterior columns and corticospinal tract in the spinal cord. The regions of the spinal cord that are first affected are the posterior columns of the cervical and thoracic segments (see Boxes 29.2 and 29.3).

### *Box 29.2* CAUSES OF VITAMIN $B_{12}$ DEFICIENCY

- Poor nutrition (e.g., vegan diet)
- Impaired absorption: autoimmune atrophic gastritis/pernicious anemia (due to lack of intrinsic factor), gastrectomy, gastric bypass, inflammatory bowel disease, ileal resection, blind loop syndrome
- Increased metabolism (neoplasm, thyrotoxicosis)

### *Box 29.3* NEUROLOGIC COMPLICATIONS OF $B_{12}$ DEFICIENCY

- Dementia
- Myelopathy
- Peripheral neuropathy
- Optic neuropathy (rare)

In addition, vitamin $B_{12}$ deficiency causes megaloblastic anemia, autonomic dysfunction (postural hypotension, infertility, and incontinence), and glossitis.

Nitrous oxide toxicity causes symptoms similar to those of vitamin $B_{12}$ deficiency. Nitrous oxide interferes with methionine synthetase, a vitamin $B_{12}$–dependent enzyme that converts homocysteine to methionine. Vitamin $B_{12}$ is also a cofactor for methylmalonyl–coenzyme A mutase. Therefore, vitamin $B_{12}$ deficiency is associated with elevated levels of homocysteine and methylmalonic acid. If vitamin $B_{12}$ deficiency is suspected but the $B_{12}$ level is normal, determination of the homocysteine and methylmalonic acid levels may aid in the diagnosis.

Selenium deficiency can cause myopathy.

Vitamin E deficiency causes peripheral neuropathy and a spinocerebellar syndrome.

Strachan syndrome is a rare myeloneuropathy thought to be related to malnutrition. It was first described in patients in Jamaica, but it has been seen in other tropical and subtropical locations as well.[2] Patients have both an optic neuropathy and a painful peripheral neuropathy. In addition to a sensorimotor neuropathy and impaired vision with central scotomas, patients can have hearing loss and mucocutaneous lesions.

In general, impaired vision and central or cecocentral scotomas are characteristic of toxic-metabolic and hereditary optic neuropathies.[3]

### 7. D

Zinc excess causes myeloneuropathy due to copper deficiency (see Table 29.1). Copper deficiency resembles vitamin $B_{12}$ deficiency. It causes paresthesias, loss of vibration and position sense, a sensory ataxia, hyperreflexia, extensor plantar responses, and a spastic gait.

*Table 29.1* SYMPTOMS DUE TO VITAMIN EXCESS

| VITAMIN | SYMPTOMS DUE TO VITAMIN EXCESS |
|---|---|
| **Vitamin A** | **Intracranial hypertension** |
| **Vitamin $B_6$ (pyridoxine)** | **Peripheral neuropathy**<br>**Lhermitte's phenomenon** |
| **Vitamin D** | **Hypercalcemia**<br>**Hypercalciuria** |
| **Vitamin E** | **Increased bleeding** |
| **Zinc** | **Myelopathy due to copper deficiency** |

### 8. D

Deficiency of copper, vitamin $B_{12}$, or vitamin E can cause myelopathy. Vitamin K deficiency causes bruising and easy bleeding.

Deficiency of copper or vitamin $B_{12}$ can occur after gastric bypass surgery. In addition, vitamin D, calcium, folate, iron, thiamine, protein, and zinc deficiencies may be present. Bariatric surgery that involves biliopancreatic diversion increases the risk for deficiencies of vitamins A, E, and K due to fat malabsorption; this is less of an issue with gastric banding.[4] Zinc deficiency can cause a rash, diarrhea, impaired immune response, and change in taste. Protein deficiency causes edema, hair loss, and poor wound healing.

Vitamin E deficiency can occur with fat malabsorption. It is also associated with ataxia with vitamin E deficiency, homozygous hypobetalipoproteinemia, and abetalipoproteinemia (Bassen–Kornzweig disease). Chronic cholestasis, pancreatic insufficiency, and α-tocopherol transfer protein deficiency can also cause vitamin E deficiency.[5] The symptoms of vitamin E deficiency resemble those of Friedreich ataxia. Patients with vitamin E deficiency have decreased reflexes, a sensory ataxia, and loss of joint and position sense (see Tables 29.2 and 29.3).

*Table 29.2* COMPARISON OF VITAMIN $B_{12}$ DEFICIENCY, VITAMIN E DEFICIENCY, AND FRIEDREICH ATAXIA

| REGION AFFECTED | VITAMIN $B_{12}$ DEFICIENCY | VITAMIN E DEFICIENCY | FRIEDREICH ATAXIA |
|---|---|---|---|
| **Corticospinal tract** | **Yes** | **No** | **Yes** |
| **Posterior columns** | **Yes** | **Yes** | **Yes** |
| **Spinocerebellar tracts** | **No** | **Yes** | **Yes** |
| **Dorsal root ganglia** | **No** | **Yes** | **Yes** |

*Table 29.3* SYMPTOMS DUE TO VITAMIN DEFICIENCY

| VITAMIN | SYMPTOMS DUE TO VITAMIN DEFICIENCY |
|---|---|
| **Vitamin A** | **Night blindness** |
| **Vitamin $B_1$ (thiamine)** | **Wernicke–Korsakoff syndrome**<br>**Beriberi including peripheral neuropathy** |
| **Vitamin $B_6$ (pyridoxine)** | **Peripheral neuropathy**<br>**Seizures** |
| **Vitamin $B_{12}$ (cobalamin)** | **Dementia**<br>**Myelopathy**<br>**Peripheral neuropathy**<br>**Autonomic dysfunction**<br>**Optic neuropathy (rare)**<br>**Megaloblastic anemia** |
| **Vitamin C** | **Scurvy**<br>**Joint and muscle pain** |
| **Vitamin D** | **Rickets** |
| **Vitamin E** | **Peripheral neuropathy**<br>**Spinocerebellar syndrome**<br>**Myelopathy**<br>**Retinitis pigmentosa** |
| **Vitamin K** | **Bleeding** |
| **Niacin** | **Pellagra** |
| **Copper** | **Myelopathy** |

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